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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

**The corresponding author has opted to make this information publicly available.*

Personal or nonessential information may be redacted at the editor's discretion.

Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office: obgyn@greenjournal.org.

Date: 05/11/2023
To: "Stephanie Alimena" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-23-753

RE: Manuscript Number ONG-23-753

Association between Timing of Colposcopy and Cervical Cancer after an Abnormal Screening Result

Dear Dr. Alimena:

Thank you for sending us your work for consideration for publication in Obstetrics & Gynecology. Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors would like to invite you to submit a revised version for further consideration.

If you wish to revise your manuscript, please read the following comments submitted by the reviewers and Editors. Each point raised requires a response, by either revising your manuscript or making a clear argument as to why no revision is needed in the cover letter.

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, and STATISTICAL EDITOR COMMENTS (if applicable) below. The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting). Upload the tracked-changes version when you submit your revised manuscript.

Your submission will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by 06/01/2023, we will assume you wish to withdraw the manuscript from further consideration.

EDITOR COMMENTS:

Dear Dr. Alimena,

Thank you for your submission. Your paper has gone through our external reviewer process and was discussed by our editorial board. We would like to give your paper additional considerations once the reviewers' comments are addressed.

In addition to the comments below, in particular please be sure to address the statistical editor's comments and recommendations regarding the issue that the cohorts are fundamentally different.

Thank you again for your submission and we look forward to receiving your revised paper.

Please also note the following:

* Help us reduce the number of queries we add to your manuscript after it is revised by reading the Revision Checklist at https://journals.lww.com/greenjournal/Documents/RevisionChecklist_Authors.pdf and making the applicable edits to your manuscript.

* All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works or need to be cited:If possible, please vary the phrasing used in lines 64-73 ("This study was...study activities.") and lines 77-85 ("KPWA included...for >37 months (MGB, PH).") which match too closely to Dr. Feldman et al.'s publication in Preventative Medicine.

* Figure 1: Please upload as a figure file on Editorial Manager.
* Figure 2: Please use color for readability. Please classify as 2A-J (each graph needs its own letter). Please move key off the graph. Please upload as a figure file on Editorial Manager.

REVIEWER COMMENTS:

Reviewer #1: In this Original Research submission, a retrospective longitudinal cohort analysis performed at 3 health systems quantified associations between time to colposcopy after an abnormal pap result and a subsequent cervical cancer diagnosis. There was no difference in future cervical cancer incidence between those who received colposcopy within 3 months and those who had colposcopy between 3 months and 1 year after abnormal cytology. Patients who did not have colposcopy within 12 months of a high-grade cytology result had a 3 times higher future risk of developing invasive cervical cancer.

Specific comments:
1. The term ">3-12 months after abnormal" is confusing to read. To me this could include "after 12 months". Please clarify; suggest "3-12 months".
2. Colposcopy within 3 months was not associated with a protective effect in any risk group including high grade cytology. Does exclusion of cancers diagnosed during the index year possibly influence this negative finding?
3. Should ASCCP and NBCCEDP recommendations regarding 3 month cytology for high grade lesions be changed based on these data?
4. Given negative findings for low-grade abnormalities, should ASCCP recommendations be modified for this cohort?

Reviewer #2: Association between timing of colposcopy and cervical cancer after an abnormal screening result

Overall this is well written and thoughtful. The authors are seeking to clarify when patients should get colpos after abnormal paps based on their risk of cancer in the time following.

Take home:
Patients who received a colposcopy >3-12 months of an abnormal result have the same risk of cervical cancer more than one year after the abnormal result as those who receive a colposcopy within 3months. Patients who did not receive colposcopy within 12 months of an abnormal result have a higher risk of subsequent cervical cancer compared to those who receive a colposcopy within 12 months.

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Thoughts / need for clarification:

In terms of the fact that of patients diagnosed with cervical cancer within 12 months, the majority (81.6%) were diagnosed within 3 months of the index test. Do you think that a confounder to this could be the fact that the provider may have told the patients they were concerned for a cancer and thus the patients were perhaps more motivated to get sooner colpo or excisional procedure?

Line 229: feels redundant to use confounding and confounders in same sentence. Revise.

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Other thoughts: picking 12 months felt somewhat arbitrary thinking that if you detected a cancer after 12 months that it was "missed" by not having an earlier colpo. But on the flip side, if a cancer was detected at 11 months, this was not included.

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I think discussing the cases of cervical cancer diagnosed within 12 months is also a good point. Also could be interesting to discuss of these were micro or macroscopic? Did the cervix appear grossly abnormal? Do we have this data?

//

Could also discuss that this gives more support to letting low grade lesions be watched in pregnancy and high-grade lesions ruled out for cancer.

STATISTICAL EDITOR COMMENTS:

Table 1: As pointed out by the Authors, these groups (based on initial management timing) were quite different (statistically) in multiple respects. The rates of cancer in the 0-12 month interval is statistically different (at $p < 0.004$ to 0.001) threshold for each pair-wise comparison. Furthermore, the groups differed w.r.t. site, age category, health insurer, comorbidity score, etc. Perhaps more importantly, the groups differed w.r.t. risk status at abnormal test, proportion with high-grade test result and most severe path in initial management period. Moreover, the difference w.r.t. completion of treatment(s) within the 12 month time frame is direct consequence of the categories of timing for their initial treatment, so not a valid statistical comparison, simply a direct result of which category those individuals were in. Need to statistically compare all baseline characteristics, including initial cancer rates. These groups clearly were not randomly allocated, but

rather it appears that those at higher risk were treated earlier.

Table 2: Based on Table 1, the rates of subsequent cancer differ, but on the other hand, total cancer counts of those with colposcopy at < 3 vs 3-12 vs > 12 were 147, 35 and 30 respectively (Again, the initial period dominates). So, to the Authors' point, it does not appear that the timing is paramount, but rather the severity of the initial cytological finding. To confound the analysis, the follow among the three cohorts differed, with higher proportion among the > 12 month group having been lost to follow-up, especially among those who had high-grade abnormalities.
Should include in the Table the median (IQR or range) times of follow-up for the three cohorts.

Table 3: Should indicate, either in Table or in footnotes, the counts for the number cases with missing data for each row entry.
Also, since the differences were NS when comparing those with low-grade and persistent mild abnormalities, and (Table 1), the proportion with high-grade abnormalities was higher in the No colposcopy < 12 month cohort, it seems that aggregating all abnormal tests results in a statistically biased comparison. Should either omit that section or corroborate it by a propensity matched (by grade etc) comparison of the three time periods of colposcopy, in order to ensure that similar cohorts are being compared.

lines 134-143: How was the assumption of proportional hazard confirmed for the three cohorts?

Fig 2: Should include, along the x-axes, the counts for the number remaining in each cohort at the designated time points.

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Sincerely,
Vivian W. Sung, MD, MPH
Deputy Editor, Gynecology

The Editors of Obstetrics & Gynecology

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Friday, June 30, 2023

Dear Dr. Wright,

Thank you for the opportunity to respond to reviewer comments on our manuscript, "Association between Timing of Colposcopy and Cervical Cancer after Abnormal Screening Result". I greatly appreciate how these reviews helped to improve the quality of the overall manuscript by contextualizing our findings with current guidelines, exploring the severity of diagnosed cancers, and clarifying study cohort nuances. Please find below this letter a point-by-point response to the reviewer and editor comments.

We updated the manuscript to highlight where our study findings may be useful for screening guideline interpretation. Our results suggest that prioritizing people with a high-grade cytology and with an otherwise unknown risk status may be prudent. We also found that receipt of colposcopy within the 3-12-month timeframe is likely safe and appropriate for those with low-grade or persistent mild abnormalities. This finding additionally suggests that colposcopy in pregnant individuals may often be able to be deferred to postpartum unless high-grade cytology results are noted and/or there are concerning clinical findings, though more research is needed on the subject before updating current guidelines.

We also added to the manuscript that most of the cancers detected in our cohort were found at an earlier stage. This finding bolsters the notion that cervical cancer screening both prevents cancer and detects cancer at an earlier, more curable stage. Indeed, the stage of cervical cancer diagnosed during follow-up was proportionately much worse for people who did not receive a colposcopy within 12 months of an abnormal test result compared to those who received a colposcopy within 12 months. We present these data in a new Supplemental Table 2.

Lastly, we elaborated on the nuances of our observational cohort study design. The size of the study cohort and the distinct types of healthcare systems represented in the cohort strengthen the generalizability of the study findings, yet also present important considerations when interpreting the data. We highlighted the differences in baseline characteristics and follow-up time observed amongst the study cohort, particularly with respect to the initial management experienced.

Thank you for your consideration of this manuscript. This manuscript has not been published or submitted elsewhere.

Sincerely,

Stephanie Alimena, MD
Division of Gynecologic Oncology
Brigham and Women's Hospital
Harvard Medical School
75 Francis St, Boston, MA 02115, United States of America
[redacted]

We would like to thank all three reviewers for their feedback and thoughtful questions. We greatly appreciate how these reviews helped to improve the quality of the overall manuscript.

Reviewer #1: In this Original Research submission, a retrospective longitudinal cohort analysis performed at 3 health systems quantified associations between time to colposcopy after an abnormal pap result and a subsequent cervical cancer diagnosis. There was no difference in future cervical cancer incidence between those who received colposcopy within 3 months and those who had colposcopy between 3 months and 1 year after abnormal cytology. Patients who did not have colposcopy within 12 months of a high-grade cytology result had a 3 times higher future risk of developing invasive cervical cancer. Specific comments:

a. The term ">3-12 months after abnormal" is confusing to read. To me this could include "after 12 months". Please clarify; suggest "3-12 months".
   Thank you for this suggestion. We updated the text, tables, and figure to reflect '3-12 months' instead of '>3-12 months' and clarified the number of days associated with each of these time intervals.
b. Colposcopy within 3 months was not associated with a protective effect in any risk group including high grade cytology. Does exclusion of cancers diagnosed during the index year possibly influence this negative finding?
   The reviewer raises an interesting question and answering the reviewer's question depends on the goal of the study. We noted if the patient was diagnosed with cancer during the index year, and then removed those cancers from subsequent analyses. This enabled us to examine whether early colposcopy affects future cancer detection (received after the index year). To answer the reviewer's question about the protective effect of earlier colposcopy on cancer treatment outcomes, we would have to look at different outcomes such as survival after the index cancer diagnosis. This is an interesting question, but it is out of scope for the present paper.
c. Should ASCCP and NBCCEDP recommendations regarding 3 month cytology for high grade lesions be changed based on these data?
   As we are the first to look at the question of colposcopy timing using real-world, observational data (to our knowledge), we think more data from other health systems are needed before amending national guidelines. Additionally, as the NBCCEDP sites are a very specific population of patients, and only one of our sites participates in NBCCEDP (Parkland-UTSW), we call on other NBCCEDP sites to study timing of colposcopy to examine reproducibility of findings before updating guidelines. One of the main findings of this study is that there are limited data to support the current guidelines. In the meantime, it still likely makes sense to prioritize high-grade abnormal results, as doing so will ensure earlier detection of prevalent cancers. We added the following text to the Discussion (lines 204-205): *While clinicians may prefer short interval follow-up after all abnormal screening results, our results suggest that prioritizing high-grade cytology and those with unknown risk status may be prudent.*
d. Given negative findings for low-grade abnormalities, should ASCCP recommendations be modified for this cohort?
   As stated above, more data from other health systems are needed to support changing guidelines. We added the following text to the Discussion (lines 205-207): *Receiving colposcopy 3-12 months after the abnormal result is likely safe and appropriate for those*

with low-grade or persistent mild abnormalities, as per ASCCP guidance published during the COVID-19 pandemic.

Reviewer #2: Association between timing of colposcopy and cervical cancer after an abnormal screening result. Overall this is well written and thoughtful. The authors are seeking to clarify when patients should get colpos after abnormal paps based on their risk of cancer in the time following. Take home: Patients who received a colposcopy >3-12 months of an abnormal result have the same risk of cervical cancer more than one year after the abnormal result as those who receive a colposcopy within 3months. Patients who did not receive colposcopy within 12 months of an abnormal result have a higher risk of subsequent cervical cancer compared to those who receive a colposcopy within 12 months. Thoughts / need for clarification:

a. In terms of the fact that of patients diagnosed with cervical cancer within 12 months, the majority (81.6%) were diagnosed within 3 months of the index test. Do you think that a confounder to this could be the fact that the provider may have told the patients they were concerned for a cancer and thus the patients were perhaps more motivated to get sooner colpo or excisional procedure?
   Yes, we agree with this great point and added the following text to the Discussion (lines 184-186): *Quicker evaluation may stem from clinicians communicating the importance of colposcopy to these patients because clinicians were more concerned about cancer due to more severe cytology/HPV results, a worrisome clinical exam, or symptoms*
b. Line 229: feels redundant to use confounding and confounders in same sentence. Revise.
   We have altered this sentence (now lines 222-223) to read more clearly now as follows: *One limitation to this study is that residual confounding may remain, although we controlled for several covariates.*
c. Other thoughts: picking 12 months felt somewhat arbitrary thinking that if you detected a cancer after 12 months that it was "missed" by not having an earlier colpo. But on the flip side, if a cancer was detected at 11 months, this was not included.
   We used 12 months because this is a metric used by several national organizations for timing of colposcopy. For example, the ASCCP risk-based guidelines use one year for their recommended timeframe for follow up. There may or may not be subtle differences between patients who have a colposcopy at 11 months versus at 12 months. However, we would not be able to study this in our cohort, because very few people were diagnosed with cancer at a colposcopy performed 11 months after the abnormal cytology/HPV result. As noted earlier, timing of colposcopy may be related to the severity of the Pap abnormality and provider concern.
d. I think discussing the cases of cervical cancer diagnosed within 12 months is also a good point. Also could be interesting to discuss of these were micro or macroscopic? Did the cervix appear grossly abnormal? Do we have this data?
   The reviewer raises an excellent point, that understanding the severity of the cancers diagnosed in this study is important. We have SEER stage information for 70.7% (n = 104/147) of cancers identified during the Initial Management Period and 60.0% (n = 39/65) of cancers diagnosed during Follow-Up. Among cancers with a known SEER stage, we found that cancer stage was significantly different among the three Initial Management Period groups, both among cancers identified during the Initial

Management Period and also Follow-Up. We added these data as Supplemental Table 2 and the following text to the Results (lines 155-158) and Discussion (lines 197-199): *Stage of cervical cancer diagnosed during the Follow-Up Period was worse for those who did not receive a colposcopy within 12 months of the index test compared to those who received a colposcopy either within 3 months or 3-12 months of an abnormal result (regional and distant stages, 43.8% vs. 6.3% and 14.3%, respectively; Supplemental Table 2)… However, most cancers were detected at earlier stages (Supplemental Table 2) supporting the idea that the screening process works both to prevent cancer and to detect early, more curable cancers.*

e. Could also discuss that this gives more support to letting low grade lesions be watched in pregnancy and high-grade lesions ruled out for cancer.
More data from other health systems are needed to support changing guidelines. Although we did not study pregnant individuals, one could consider delaying colposcopy for pregnant individuals with low-grade abnormalities based on our findings and prior data on the very small number of cancers found among non-pregnant patients with low-grade results. The goal of colposcopy during pregnancy is to ensure that no invasive cancer is present, and in the absence of this, colposcopy and/or treatment of pre-invasive disease is deferred to postpartum. We added the following text to the Discussion (lines 208-212): *Future research should also study if colposcopy in pregnant individuals can be deferred to postpartum unless high-grade cytology results are noted and/or there are concerning clinical findings. Prior studies support that most cancers are found among patients with high-grade cytology results, and as precancers are not generally treated during pregnancy, this might be an acceptable group to delay evaluation of low-grade abnormalities, after more research on the subject.*

STATISTICAL EDITOR COMMENTS:

a. Table 1: As pointed out by the Authors, these groups (based on initial management timing) were quite different (statistically) in multiple respects. The rates of cancer in the 0-12 month interval is statistically different (at $p < 0.004$ to 0.001) threshold for each pair-wise comparison. Furthermore, the groups differed w.r.t. site, age category, health insurer, comorbidity score, etc. Perhaps more importantly, the groups differed w.r.t. risk status at abnormal test, proportion with high-grade test result and most severe path in initial management period. Moreover, the difference w.r.t. completion of treatment(s) within the 12 month time frame is direct consequence of the categories of timing for their initial treatment, so not a valid statistical comparison, simply a direct result of which category those individuals were in. Need to statistically compare all baseline characteristics, including initial cancer rates. These groups clearly were not randomly allocated, but rather it appears that those at higher risk were treated earlier.
The editor raises the important consideration that this study is based on observational data, so people were not randomly allocated to the initial management groups. We updated the Methods (lines 115-116) to clarify that all baseline characteristics were statistically compared, which are reported in the Table 1 and Supplemental Table 1 footnotes.

b. Table 2: Based on Table 1, the rates of subsequent cancer differ, but on the other hand, total cancer counts of those with colposcopy at < 3 vs 3-12 vs > 12 were 147, 35 and 30 respectively (Again, the initial period dominates). So, to the Authors' point, it does not

appear that the timing is paramount, but rather the severity of the initial cytological finding. To confound the analysis, the follow among the three cohorts differed, with higher proportion among the > 12 month group having been lost to follow-up, especially among those who had high-grade abnormalities. Should include in the Table the median (IQR or range) times of follow-up for the three cohorts.

The editor raises important points. We added the median time-to-follow-up data to the Table 2 footnotes to comply with the journal formatting request to minimize mixing the types of data reported (e.g., presenting counts and row percentages in the same table as median and interquartile ranges).

c. Table 3: Should indicate, either in Table or in footnotes, the counts for the number cases with missing data for each row entry. Also, since the differences were NS when comparing those with low-grade and persistent mild abnormalities, and (Table 1), the proportion with high-grade abnormalities was higher in the No colposcopy < 12 month cohort, it seems that aggregating all abnormal tests results in a statistically biased comparison. Should either omit that section or corroborate it by a propensity matched (by grade etc) comparison of the three time periods of colposcopy, in order to ensure that similar cohorts are being compared.

   We updated the Methods (lines 126) to clarify that all patients were included in the model, as all patient covariates included in the model were known (i.e., there were no missing data); additionally, the total counts used in the models are reported in the Table 3 footnotes. We adjusted the model including all results by cytology severity, in addition to adjusting for the other covariates also used in the cytology severity-stratified models (age, risk, site) and reported this in the Table 3 footnotes. We re-executed the model containing all results among propensity matched cohorts (based on age, risk status, result severity, and site) and found nearly identical hazard ratios, which we suspect is because the original models were adjusted for result severity.

d. lines 134-143: How was the assumption of proportional hazard confirmed for the three cohorts?

   We assessed proportional hazards by including time-dependent covariates, created as interactions of the predictors (age group at index test, risk status at index test based on prior cervical cancer screening history, severity of cytology result from the index test, and healthcare system) and a function of survival time, in the model. All time-dependent covariates were not significantly associated with the outcome at $p<0.05$, and thus did not violate the proportional hazards assumption. We updated the Methods (lines 128-129) to clarify this.

e. Fig 2: Should include, along the x-axes, the counts for the number remaining in each cohort at the designated time points.

   Thank you for this suggestion. We updated Figure 2 to report these numbers.