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Dear Editor,

We are extremely grateful for the valuable comments and suggestions provided by the reviewers who generously took time to kindly help us revise the manuscript. We do take their efforts with sincere appreciation and have done for all of the comments as in the revised MS entitled **"Retinoic acid receptor beta (*RARβ*) promoter methylation and risk of cervical cancer" Manuscript NO.:** 36548. The MS was polished and all English language approved by native mother toung of The Charlesworth Author Services Team at UK as attached certificate.

Since significant changes were made to incorporate recommendations by the reviewer, we used the red color tract-change in this resubmission.

We would now like to resubmit it once again to World Journal of Virology. All authors have approved this revised manuscript. We do hope that all correction have met the reviewers' recommendations and would like to thank you in advance for your kind consideration.

Sincerely yours,

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Responsed to reviewer

Reviewer #1: 1. The 2nd and 3rd sentences of the abstract, the biological connection between HPV infection and hypermethylation needs to be clarified or justified.

Answer: We clarified by rephrasing these sentences in abstract lines 3-6.

2. On page 8 in the middle of the page, "Several studies have found that DNA methylation frequently occurs in cervical cells but rarely in normal cells, suggesting that aberrant methylation may indicate risk of cancer development." This statement is rather confusing. For one, DNA methylation is a modification that happens in both normal and cancer cells. For two, the "aberrant methylation" was not defined. Hypermethylation?

Answer: We rephrase these sentences as "Several studies have found that DNA methylation frequently occurs in cervical cells but rarely in normal cells, suggesting that their methylation is highly related to the severity of cervical neoplasia".

3. In general, methylation vs hypermethylation is not clearly defined and differentiated, which complicated data interpretation throughout the review.

Answer: We change "hypermethylation" to "methylation."

Reviewer #2: Revision manuscript n. 36548 entitled: Retinoic acid receptor beta (RARβ) promoter methylation and risk of cervical cancer The authors of this review give an overview of the most recent works on retinoic acid receptor ß promoter methylation and its relationship with progression of cervical cancer lesions and tumor development. Although, the methylation of a single gene is not sufficient to explain the complex process of cell transformation and cancer development, the majority of the study published so far suggest that the hypermethylation of RARβ gene may have a role in cervical carcinogenesis. The review is quite clear and easy to follow; however, some corrections are required:

Abstract: Line2, replace, "underdeveloped" with "developing"

Answer: We change abstract line2 as reviewer suggestion.

Core tip: place a comma after "Thus"

Answer: We placed a comma in core tip as reviewer suggestion.

Paragraph "Genome of HPV": Line 5, correct "later" with "late"
Replace "at least 30 genotypes" with "at least 40 genotypes"

Answer: We change words in paragraph "Genome of HPV" as reviewer suggestion.

Insert page number Last conclusive paragraph:

Answer: We insert page number as reviewer suggestion.

"Although DNA methylation of only one gene may not represent of the…", delete "of" before "the".

Answer: We deleted "of" as reviewer suggestion.

Reviewer #3: Although there have contradictory findings, most studies indicate that downregulation of RARβ expression and its epigenetic methylation show prognostic roles in cervical cancer. Thus, this review manuscript gave an overall background of cervical cancer and its risk factors focusing on HPV and RARβ. The contents of current manuscript might promote understanding of cervical cancer etiology, particularly the RARβ. Minor comments for improvement of comprehension were appended.
1. Not only one biomarker can be helpful in disease prediction. Since RARβ and TSGs are focuses of this manuscript, the information of additional combinatory candidates other than RARβ is helpful.

Answer: We agree with the reviewer that one biomarker may not be a good predictive factor for cancer progression. Several researchers have investigated methylation of multiple genes aiming to identify the sets of biomarkers that best predict the progression of severing diseases (please see examples below). Some articles included RARβ in their panel, whereas others studied other genes. The objective of our study is to identify the relationship of RARβ silencing and cervical cancer, therefore, we focus on this topic.

Article 1.
Yang N, Nijhuis ER, Volders HH, Eijsink JJ, Lendvai A, Zhang B, et al. Gene promoter methylation patterns throughout the process of cervical carcinogenesis. Cell Oncol. 2010;32(1-2):131-43. doi: 10.3233/CLO-2009-0510.

Article 2.
Wu JH, Liang XA, Wu YM, Li FS, Dai YM. Identification of DNA methylation ofSOX9 in cervical cancer using methylated-CpG island recovery assay. OncolRep. 2013 Jan;29(1):125-32. doi: 10.3892/or.2012.2077. Epub 2012 Oct 9. PubMed PMID:23064448.
Article 3.
Siegel EM, Riggs BM, Delmas AL, Koch A, Hakam A, Brown KD. Quantitative DNA methylation analysis of candidate genes in cervical cancer. PLoS One. 2015 Mar 31;10(3):e0122495. doi: 10.1371/journal.pone.0122495. eCollection 2015. PubMed PMID: 25826459; PubMed Central PMCID: PMC4380427.

2. The correlation between HPV and RARβ methylation is interesting.

Answer: It is very interesting to dissect the gene interaction networks to determine the relationship between host epigenetic silencing with the molecules related to HPV infection in the development of cervical cancer. However, this area is very complex and needs to be further elucidated.

3. Epigenetic modification of genes consists of several mechanisms. Though the title focused on promoter methylation, other kinds of RARβ epigenetic modification could further highlight its importance and clinical relevance.

Answer: We agreed with the reviewer and mentioned on the manuscript page 12-13 that some studies have revealed other silencing mechanisms apart from promotor methylation. They highlighted that although DNA methylation was the major epigenetic mechanism for gene silencing, repressive histone modifications also played an independent role in the control of gene expression. To the best of our knowledge, other silencing mechanisms relating to RARβ gene investigated so far have been incorporated in this manuscript.