



Does the vaginal microbiome drive cervical carcinogenesis?

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Mini-commentary on BJOG-19-0278.R1: The vaginal microbiota, HPV and cervical dysplasia: a systematic review and network meta-analysis

Does the vaginal microbiome drive cervical carcinogenesis?

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Since the discovery of lactic acid producing bacteria in the vagina by Albert Dodelein in 1892, multiple studies have explored the relationship between the vaginal microbiota and various physiological, infectious and malignant conditions (Łaniewski et al, *Sci Rep.* 2018;8(1):7593). Whether the vaginal microbiome influences the association between human papillomavirus (HPV) infection and cervical cancer is one example with several, albeit small studies assessing whether vaginal dysbiosis influences HPV acquisition, persistence and progression to cervical dysplasia and malignancy. Whilst findings from these studies have been consistent and highly suggestive of an altered vaginal microbiome (Brusselsaers et al., *Am J Obstet Gynaecol*

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2019; 221(1):9-18), compelling evidence for the specific bacterial community state type (CST) species linked with cervical disease is lacking.

Genital HPV infections, though common in young sexually active women, are mostly transient and resolve without ever causing disease. Factors that influence their acquisition and especially persistence are not yet fully understood although smoking, the pathogenicity of specific HPV subtypes and immunological factors are important (Crosbie et al., *Lancet* 2013;382:889–99). It is indeed plausible that women with certain vaginal microbiome CST groups are more prone to acquiring and failing to clear high risk HPV and therefore identifying these CSTs is important to 1). Predict cervical cancer risk 2). Develop targeted prevention strategies, and 3). Test novel therapeutic strategies based on pre/probiotics.

Norenhag et al. in a systematic review and network-analysis of eleven cross sectional and longitudinal studies sought to explore what subtypes of CST, defined by molecular techniques, are linked with HPV-infection and cervical disease and report that non-lactobacillus species or *Lactobacillus iners* had 3-5 times higher odds of any prevalent HPV and 2-3 times higher odds for high risk HPV, cervical dysplasia and cervical cancer in comparison to *Lactobacillus crispatus* (Norenhag et al, *BJOG* 2019). These findings stem from a well-designed systematic review addressing a clearly focused question and conducted according to the PRISMA guidelines. Nevertheless, they should be interpreted with caution given the substantial methodological and population heterogeneity across included studies and the ever present possibility of reverse causation, especially with the inclusion of cross sectional studies. The variability in the composition of CSTs across studies, lack of consensus on methods of CST classification, omission of CSTs not fitting with authors' categories and use of varying terminologies for different disease stages are important limitations.

Importantly, quality assessment of included studies did not address how confounding variables including co-infection with HIV were addressed, especially for those studies involving high risk women (sex workers), nor was there clarity on how decisions on the overall quality of included studies were made. Despite these shortcomings, however, the study does provide a unique perspective into the role of specific CTS subtypes in cervical carcinogenesis. Well-designed longitudinal studies with adequate sample sizes and using standardized sampling and analytical methods are now needed to provide robust evidence on what CST subtypes are linked with high risk HPV and cervical cancer and importantly, to confirm causality.

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