Genital tract microbiota composition profiles and use of prebiotics and probiotics in gynaecological cancer prevention: review of the current evidence, the European Society of Gynaecological Oncology prevention committee statement

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Female genital tract (FGT) microbiota has been associated with the development of gynaecological cancers. Thus, the possibility of whether manipulation of the FGT microbiota can help in the prevention of disease should be investigated. Various prebiotics, probiotics, and other non-clinician prescribed agents have been reported to have therapeutic effects in cervical disease. Numerous studies have reported an association between human papillomavirus infection and subsequent cervical dysplasia and a decrease in the abundance of *Lactobacillus* species. A continuum of microbiota composition is observed from the vagina to the upper parts of the FGT, but no evidence suggests that manipulation of the vaginal microbiota can help to modify the composition of other FGT compartments. Although prebiotics and probiotics have been reported to be beneficial, the studies are small and of varying design, and high-quality evidence to support their use is lacking. Currently, no studies have examined these therapeutics in other gynaecological malignancies. Thus, recommendation of probiotics, prebiotics, or other over-the-counter supplements for the prevention of gynaecological cancers warrants larger, well designed studies.

Introduction

This European Society of Gynaecological Oncology consensus statement aims to provide a summary of current evidence regarding the role of the female genital tract (FGT) microbiota in gynaecological cancers and pre-invasive disease from studies using next-generation sequencing (NGS) techniques and the use of prebiotics, probiotics, and other non-clinician prescribed agents in relation to these conditions. Here, we summarise the existing literature on this important topic (figure 1).

The microbiome

The human microbiome encompasses microorganisms, their genomes, and their surrounding chemical environment within the human body. The term microbiota is used to refer to the microorganisms alone. NGS techniques based on the bacterial 16S rRNA genes permit in-depth study of microbial community structures unlike standard culture-based microbiological techniques. Advances in sequencing techniques have resulted in rapidly evolving research on the human microbiome and its role in health and disease. In addition, recognition of the variation in microbiota composition among individuals is expanding our understanding of the pathophysiology underlying various diseases affecting different body systems.[1–3] Through the production of bioactive compounds and metabolites, the microbiome can modify host cell signalling and immune pathways that impact tissue survival, homoeostasis, and function. Pathogenic bacteria secrete virulence factors to colonise and establish themselves within the body systems, including the vagina, and use enzymes and proteins such as haemolysin and sialidases to form cellular adhesions, biofilms, and short-chain fatty acids. They can activate inflammatory and oxidative stress pathways causing host DNA damage,[4,5] which is implicated in both development of,[1,2,6–12] and protection against, malignancies[13–15] including those of the FGT.

FGT microbiome

The bacterial colonisation of the vagina with *Döderlein's Bacillus*, which we now recognise to be *Lactobacillus* species, was first described by the German obstetrician Albert Döderlein in 1892. He further described the antagonistic relationship between these bacteria and *Staphylococcus* spp and its bactericidal properties relating to its ability to produce lactic acid.[16] Indeed, many studies have shown that the presence of *Lactobacillus* species in the FGT might reduce the risk of bacterial infections caused by *Chlamydia trachomatis*,[17] viral infections including those caused by HIV,[18] and obstetric complications, including miscarriage and preterm birth.[19,20]

Bacterial vaginosis, a common condition known to clinicians, is a polymicrobial disorder characterised by an abundance of anaerobes, particularly *Gardnerella*, *Prevotella*, and *Peptostreptococcus* species and concomitant depletion in *Lactobacillus* spp abundance.[21] Bacterial vaginosis has previously been associated with the development of cervical intraepithelial neoplasia, and the incidence, prevalence, and persistence of its causative agent, human papillomavirus (HPV).[22–25]

In 2011, Ravel and colleagues[26] were the first group to perform NGS using bacterial 16S rRNA genes to characterise the vaginal microbiota using vaginal swabs from 396 ethnically diverse asymptomatic women of reproductive age. Hierarchical taxonomic clustering analysis was used to classify the vaginal microbial composition of individuals

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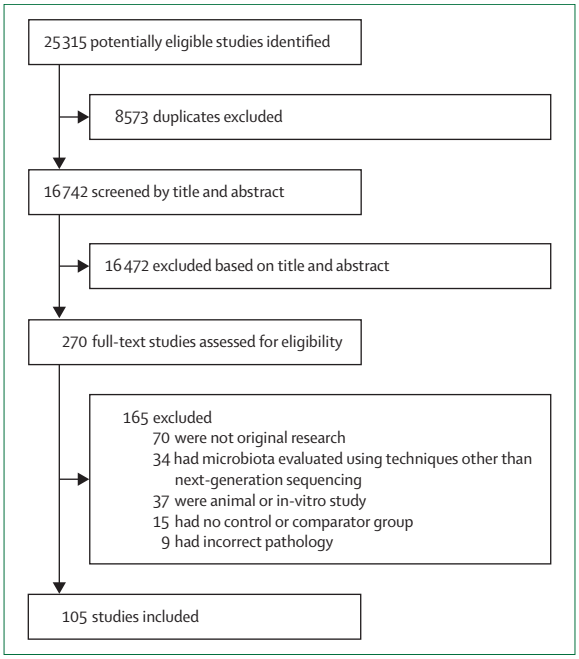

Figure 1: **Flowchart for study selection**

into one of five community state types (CSTs). CST I is characterised by the dominance of *Lactobacillus crispatus*, II by that of *Lactobacillus gasseri*, III by that of *Lactobacillus iners*, and V by that of *Lactobacillus jensenii*, and tend to have low species diversity and evenness. In contrast, CST IV is typically devoid of *Lactobacillus* spp and is instead enriched with obligate anaerobic species such as *Gardnerella* spp, *Megasphera* spp, *Sneathia* spp, and *Prevotella* spp, that are often associated with bacterial vaginosis. Such classification systems have subsequently been used in numerous other studies, allowing for comparison of results at a basic level. The healthy vulvar microbiota has been studied and shows similarities with the vaginal, cutaneous, and gastrointestinal microbiota comprising *Lactobacillus*, *Corynebacterium*, *Staphylococcus*, and *Prevotella* taxa.[27]

See Online for appendix

Cancers of the lower FGT are predominantly HPV-related, whereas those of the upper FGT are HPV-unrelated. Research interest in understanding the role of the vaginal microbiota in cervical disease is increasing, with 61 studies conducted using NGS being published over the last decade.

Although the majority of the FGT microbiota resides within the vagina, the upper FGT is certainly not sterile. The microbiota of the cervical canal, uterus, fallopian tubes, peritoneal fluid, and vagina was sequenced by Chen and colleagues[28] who found a continuum of the microbiota composition along the FGT with decreasing *Lactobacillus* abundance from the vagina to the fallopian tubes, a finding corroborated by other studies.[29,30] The uterus facilitates transport of sperm from the cervical canal to the uterine corpus through a peristaltic-like action that might also enable transport of vaginal and cervical microbiota.

Researchers have begun to investigate the putative role of the low number of microorganisms found in the endometrium and ovary in the context of endometrial and epithelial ovarian cancers. Inherited genetic predisposition is the cause of only a few endometrial and epithelial ovarian cancers; thus, other factors are responsible for the malignant transformation. Epidemiological data have shown strong correlations between pelvic inflammatory disease, ovarian (mostly serous) cancer or pre-invasive or borderline disease, and endometrial cancer or pre-invasive or borderline disease.[31–33] Studies have also revealed distinct microbiome signatures that might contribute to increased susceptibility to epithelial ovarian cancer[34] and endometrial cancer.[30]

Researchers are yet to reach a consensus regarding the composition of a healthy endometrial microbiota. Although many groups have reported the predominance of *Lactobacillus*, some studies have reported it to be absent, or in low abundance.[35] The ovarian microbiome is even less well characterised than the endometrial microbiome. The ovarian and fallopian tube microbiota have low biomass of microorganisms; thus, sufficient 16s rRNA sequences for analysis cannot be obtained.[30] Nevertheless, these sites are also in continuation with the lower FGT in addition to the peritoneal cavity, both of which represent sources of bacteria. Furthermore, the microbiota composition of the control group has been mainly reported in studies using samples from women undergoing surgery for benign conditions, including uterine fibroids, uterine prolapse, and benign ovarian cysts, which might not accurately represent the composition of a healthy individual, warranting further research (appendix pp 10–13).

Prebiotics and probiotics

A therapeutic and commercial interest in the production of supplements, such as prebiotics and probiotics, has rapidly developed because the microbiota is associated with human health.

Probiotics are defined by WHO as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. They have the potential to improve health and disease outcomes by favourably altering the microbiota composition. Probiotics, together with traditional antibiotics,[36] have been shown to improve the cure rates of bacterial vaginosis and prevent its recurrence through their ability to increase the abundance of *Lactobacillus* spp, although the evidence is controversial.[37] A meta-analysis of 22 randomised controlled trials suggests that probiotics are most effective when used in combination with antibiotics, to treat bacterial vaginosis. However, these studies did not follow up the included patients in the long-term.[38]

Prebiotics are indigestible carbohydrates, including those from the fructo-oligosaccharide and gluco-oligosaccharide families, which promote the growth of healthy bacteria already present in the body. They have been most well studied in the gastrointestinal tract,

where they have been shown to modulate microbiota composition, and exert immunomodulatory effects independent of the microbiota.[39] Several in-vitro studies and a few small in-vivo studies suggest proof of concept of prebiotics for modulation of the vaginal microbiome. Fructo-oligosaccharides and gluco-oligosaccharides have been shown to promote the growth of *L crispatus*, *L jensenii*, and *Limosilactobacillus vaginalis* in vitro, but not that of *Candida albicans*, *Escherichia coli*, or *Gardnerella* spp. The researchers used high performance liquid chromatography to show that gluco-oligosaccharides and fructo-oligosaccharides could not be used as energy sources by *C albicans*, *E coli*, or *Gardnerella* spp.[40] Gluco-oligosaccharide, applied as an intravaginal gel immediately after metronidazole treatment for bacterial vaginosis, has been shown to considerably reduce Nugent scores (a Gram-based scoring system for the diagnosis of bacterial vaginosis) at 8 days and 16 days of treatment in a randomised controlled trial of 42 women.[41]

Other non-clinician prescribed agents, including micronutrients (for example, zinc and phytonutrients such as 3,3′-diindolylmethane and epigallocatechin gallate), have been marketed to promote gynaecological health, and those related to the prevention of gynaecological cancers have not been included in previous reviews.

Female genital tract microbiome and gynaecological cancers

The current evidence regarding the role of the FGT microbiota in gynaecological cancers and pre-invasive disease is summarised in the appendix pp (1–18). 61 studies describe the cervicovaginal microbiota relating to HPV or cervical pre-invasive and invasive disease as presented in the appendix pp (1–10). Although there is considerable heterogeneity among the studies regarding the specific anaerobes related to the presence of HPV or cervical pre-invasive disease, the consensus is that both viral persistence and pre-invasive lesions are associated with a decrease in the abundance of *Lactobacillus* spp and an increase in vaginal microbiota diversity. The anaerobic species most frequently associated with disease were *Prevotella* (19 studies), *Gardnerella* (16 studies), *Sneathia* (14 studies), *Fannyhessea* (previously *Atopobium*[42]; nine studies), *Anaerococcus* (seven studies), and *Streptococcus* (seven studies). Figure 2 depicts the number of participants in each study. Studies reporting the use of linear discriminant analysis effect size (LEfSe) analysis to identify the operational taxonomic units responsible for the differences between study groups have been further described to show the number of significant taxa at all taxonomic levels (figure 2B), the number of *Lactobacillus* genera and species enriched in controls relative to people with disease, and the number of pathogenic anaerobic genera and species enriched in those with disease relative to controls (figure 2C, D).

A network meta-analysis of 11 studies published in 2019 concluded that compared with a *L crispatus*-dominant vaginal microbiota, a *Lactobacillus* spp-depleted vaginal microbiota or *L iners*-dominant vaginal microbiota were three to five times more likely to be HPV-positive and two to three times more likely to be associated with high-risk HPV infection and cervical dysplasia or cancer.[43]

A single study relating to the vaginal microbiota in women with vaginal pre-invasive and invasive disease was identified (appendix pp 1–10). Consistent with the abundance patterns in other FGT compartments, the abundance of some anaerobic bacteria including *Fannyhessea*, *Gardnerella*, *Allobaculum*, and *Clostridium* ($p<0·05$) was higher in women with the disease than in the controls.

We identified one study investigating the intratumoral microbiota of invasive vulval squamous cell carcinoma in relation to clinical outcomes after surgical treatment. Although 16S rRNA sequencing was performed, the sequencing data were not reported. However, the study reported that the higher abundance of *Fusobacterium nucleatum* ($p=0·048$) and *Pseudomonas aeruginosa* ($p=0·042$) detected using quantitative PCR techniques was related to a shorter time to progression after initial surgical treatment (appendix pp 1–10).

Six studies have reported the endometrial and vaginal microbiota relating to endometrial cancer, in comparison with the microbiota of women undergoing surgery for benign gynaecological conditions (appendix pp 10–11). No consensus was reached on whether endometrial microbiota diversity increased or decreased in the presence of malignancy. Nonetheless, studies reported increased abundance of anaerobes such as *Fannyhessea* (one study), *Porpyromas* (two studies), *Prevotella* (two studies), and *Pseudomonas* spp (one study), albeit the studies being heterogeneous. The vaginal microbiota of women with endometrial cancer could be differentiated from that of women in the control group, on the basis of the increased relative abundance of the aforementioned taxa.

The role of ovarian and vaginal microbiota in women with epithelial ovarian cancer compared with that in controls undergoing surgery for benign gynaecological conditions has been assessed in eight studies (appendix pp 11–13). Similar to previous findings, anaerobic species were predominant in ovarian cancer samples with no consensus regarding any specific species. *Acinetobacter* spp was the only genus identified in more than one study, and it was more abundant in ovarian tissue from women with cancer than in the control group (three studies). Figure 3 shows the number of participants in each study along with the number of significant taxa, *Lactobacillus*, and pathogenic anaerobic genera and species shown by LEfSe analysis in vaginal, vulvar, endometrial, and ovarian disease.

Prebiotics, probiotics, and other agents in gynaecological cancers

Prebiotics and probiotics

11 studies investigated the use of prebiotics and probiotics for the prevention of HPV-induced cervical malignancy: six studies used two commercially available

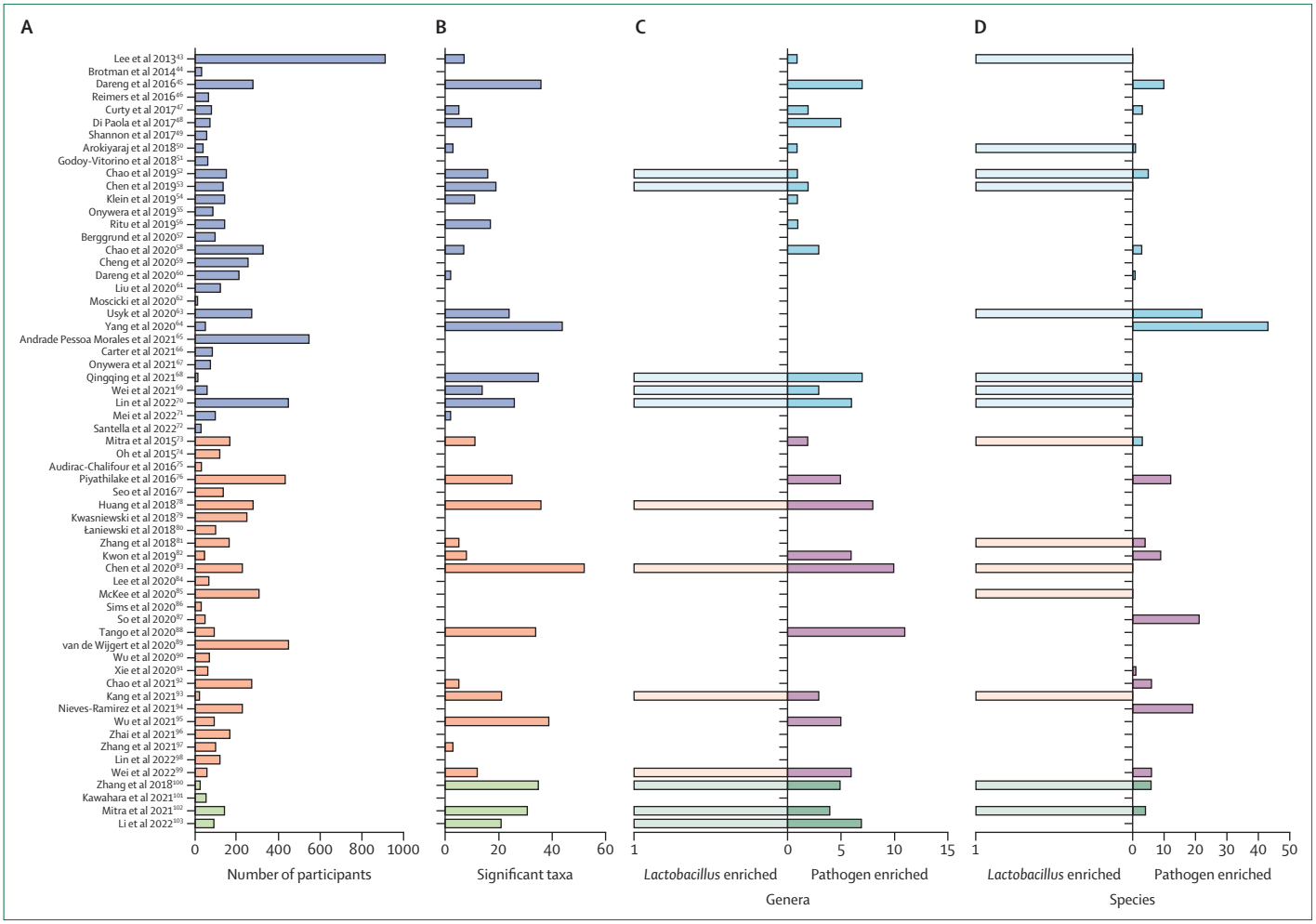

Figure 2: **Summary of studies reporting the composition of the vaginal microbiota according to HPV-related outcomes (blue), studies reporting cervical disease with or without HPV-related outcomes (orange), and before and after cervical treatment (green)**

(A) Number of participants per study. (B) Number of significant taxa identified by LEfSe analysis at all taxonomic levels. (C, D). Number of *Lactobacillus* genera and species enriched in controls relative to those with disease, and the number of pathogenic anaerobic genera and species enriched in those with disease relative to controls. References are found in the appendix. HPV=human papillomavirus. LEfSe=Linear discriminant analysis effect size.

topical vaginal prebiotic-containing preparations[44–49] and five studies used preparations containing probiotics, including *L casei* strain Shirota, *L crispatus,* and *L rhamnosus* both alone and in combination with *L reuteri*.[50–54] Among the five studies involving probiotic preparations, four studies examined oral probiotics containing *L casei* strain Shirota, *L crispatus* M247, and *L rhamnosus* GR-1 combined with *L reuteri* RC-14,[50–52,54] and one study examined a topical vaginal probiotic preparation containing *L rhamnosus* BMX 54.[53] Studies of the prebiotic preparations showed promising results. The effect of prebiotics on HPV clearance was investigated in four studies, three of which showed an increased rate of clearance of HPV infection following treatment.[44,46,47] Five studies investigated the rates of cytological and colposcopic clearance of abnormalities, and all showed positive results following prebiotic treatment.[44–46,48,49] One study assessed the histological outcomes and showed an increased rate of histological clearance following treatment.[46] The duration of use of these prebiotic-containing preparations ranged from 2 to 12 months. None of the studies included a placebo arm, and only one study, by Di Pierro and colleagues,[51] reported on the vaginal microbiota composition of participants before and after treatment. In this cohort studied by Di Pierro and colleagues, none of the 35 participants had an *L crispatus*-dominant vaginal microbiota at baseline, but after 3 months of treatment with the *L crispatus* M247 probiotic, 33 (94%) of 35 participants had switched to a *L crispatus*-dominant vaginal microbiota, as shown using Illumina MiSeq. Of the five studies investigating probiotics in cervical disease, only one showed increased rates of HPV clearance following treatment with *L rhamnosus,*[53] and four reported increased rates of clearance of cytological abnormalities.[50,52–54] The duration of administration ranged from 3 to 12 months or, in one study, until the high-risk HPV DNA test yielded negative

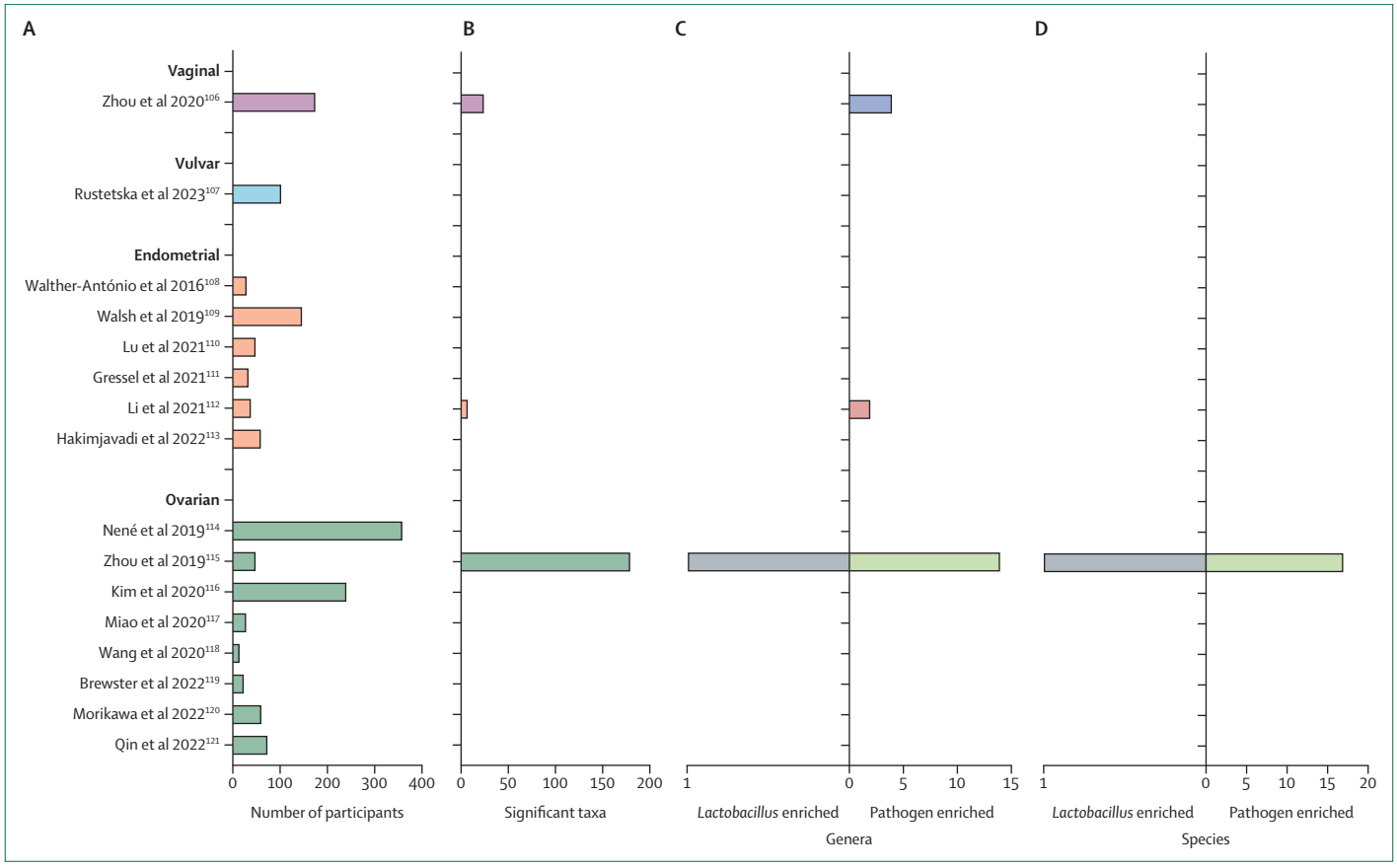

Figure 3: **Summary of studies reporting the composition of the microbiota in vaginal (purple), vulval (blue), endometrial (orange), and ovarian disease (green)**
(A) Number of participants per study. (B) Number of significant taxa identified by LEfSe analysis at all taxonomic levels. (C, D) Number of *Lactobacillus* genera and species enriched in controls relative to those with disease, and the number of pathogenic anaerobic genera and species enriched in those with disease relative to controls. References are found in the appendix. LEfSe=Linear discriminant analysis effect size.

results.[52] One of the five studies reported the use of a placebo agent.[52] The size of the study cohorts ranged from 35 to 160 women (figure 4). We were unable to identify any studies investigating the use of prebiotics or probiotics for the prevention of endometrial, epithelial ovarian, vulval, or vaginal malignancy (appendix pp 13–18).

Other non-pharmacological agents

Apart from prebiotic and probiotic preparations, several other non-pharmacological oral and vaginally administered agents are available without a clinician's prescription and have been investigated for potential activity in HPV clearance or regression of low-grade cervical lesions. These agents include active hexose correlated compound,[55] beta-carotene,[56–60] 3,3′-diindolylmethane,[61–63] epigallocatechin gallate,[64,65] indole-3-carbinol,[66] Praneem polyherbal tablet,[67] silicon dioxide with sodium selenite and citric acid,[68,69] and zinc[70,71] (appendix pp 13–18). The size of the study cohorts ranged from 20 to 551 participants, and the duration of administration, when stated, ranged from 1 month to 2 years. 12 studies included a placebo-treated control group. The study involving the use of active hexose correlated compound and two studies investigating the use of zinc showed increased rates of HPV clearance following treatment.[55,70,71] Clearance of cytological abnormalities was observed following the use of silicon dioxide with sodium selenite and citric acid[68] and zinc.[70] Increased rates of histological regression were observed in three studies using silicon dioxide with sodium selenite and citric acid,[69] indole-3-carbinol,[66] and 3,3′-diindolylmethane;[61] however, two studies using 3,3′-diindolylmethane did not show positive results.[62,63] A study investigating epigallocatechin gallate also reported increased rates of regression (mixed histological and cytological results) following treatment.[64] The remaining studies did not yield positive results.

Opinion and recommendations

Studies exploring the genital tract microbiome in gynaecological cancer and pre-invasive disease suggest that a high-diversity *Lactobacillus*-depleted microbiota is associated with disease states, with various anaerobes highlighted as differentially abundant. The studies, however, show an unexplained heterogeneity, particularly in terms of the differentially expressed anaerobes. Vaginal microbiota composition is known to be influenced by

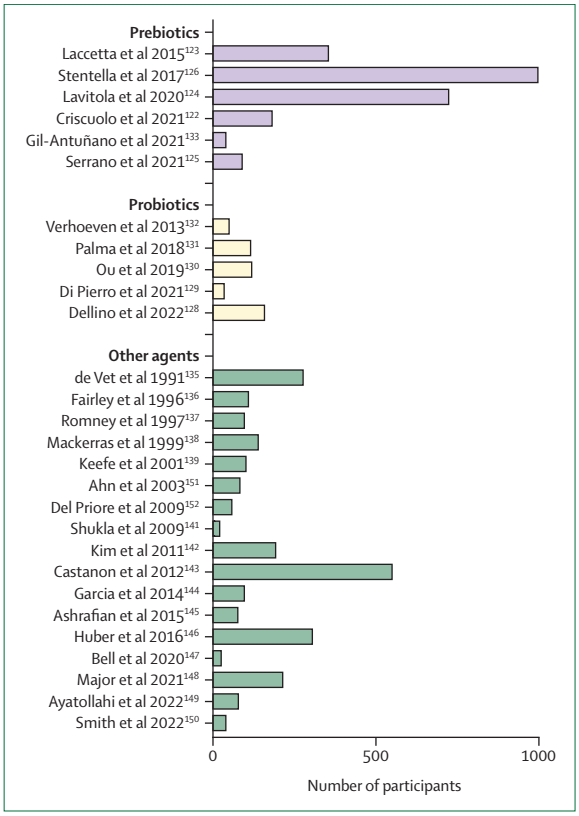

Figure 4: **Number of participants in studies reporting the use of prebiotics, probiotics, and other supplements for human papillomavirus and cervical disease**

References are found in the appendix.

both non-modifiable and modifiable risk factors. Black, Hispanic, and Asian ethnicity and a postmenopausal status are non-modifiable risk factors for a *Lactobacillus*-depleted, pathogen-enriched vaginal microbiota. Modifiable risk factors for the vaginal microbiota include cigarette smoking, douching, obesity, and sexual intercourse. Many of these variables are also risk factors for gynaecological cancers, and therefore the interplay between these factors, vaginal microbiota composition, and cancer risk warrants further investigation. Furthermore, the menstrual cycle can result in variations in vaginal microbiota composition, with a typically high-diversity population with low levels of *Lactobacillus* during menstruation. The influence of these variables on the upper FGT microbiome has not yet been studied. Nevertheless, these risk factors differ between study populations, which along with differences in sequencing data analysis might partly explain the inter-study heterogeneity observed. A large, international, multicentre study could help to understand this aspect further.

Although data from longitudinal datasets and intervention studies indicate that vaginal microbiota composition can help to identify the regression or progression of cervical pre-invasive disease, evidence that suggests causality is inconclusive. Furthermore, whether the disease drives this change in the microbiome, or whether the microbiome contributes to disease development remains unclear. Numerous studies have linked changes in the FGT microbiome to pathways involved in the hallmarks of cancer described by Hanahan and Weinburg.[72] Chronic inflammation can occur as a result of an altered microbiome composition and is a well described driver of neoplastic pathways involved in cellular metabolism and proliferation, apoptosis, genomic instability, viral integration, angiogenesis, and cellular migration required for metastasis.[73]

Interactions between different types of vaginal bacteria can be both synergistic and antagonistic. *Lactobacillus* spp can inhibit the growth of anaerobic pathogens, such as *Prevotella* and *Gardnerella* spp, through production of lactic acid, which helps to maintain a low pH, and production of bacteriocins, which are bacteriostatic and bactericidal proteins that directly prevent pathogen survival, and biosurfactants, which help to break down the biofilms often formed by pathogenic anaerobes, particularly *G vaginalis*.[16,74,75] *L crispatus*, when present, is usually strongly dominant, infrequently coexists with other bacterial species, especially anaerobes, and is the least likely to transition to CST IV, which suggests that this bacterium is highly resistant to co-colonisation with other species and hence might be frequently associated with health states.

An interplay between the presence of bacteria and viruses might exist, both in a general biological context and within the specific domain of cancer. HPV is known to be the causative agent in over 99% of cases of cervical cancers, and the presence of bacterial vaginosis has long been cited as a risk factor for incident and persistent HPV infection. A dysbiotic microbial population rich in pathogenic anaerobes and depleted of *Lactobacillus* promotes an environment that can diminish the virus-trapping characteristics of the cervical mucus, decrease cell integrity, aid HPV entry into cervical cells, promote viral integration, and alter cellular proliferation and metabolism.[76] Nevertheless, how the interactions between the bacterial environment, viruses, and the host change throughout the course of disease progression has not been studied and warrants further investigation. Furthermore, whether different microbiota associations exist in specific histological subtypes of FGT cancers remains unclear. A comprehensive understanding of the pathophysiology of these incompletely understood diseases as well as the preventive and therapeutic potential is an exciting prospect.

Several mechanisms have been proposed to explain how probiotics exert their effect on the microbiome. These mechanisms include the establishment of a probiotic population, enhancement of endogenous and exogenous *Lactobacillus* spp growth through production of lactic acid and other key metabolites that support their growth, direct immunomodulation of the intrinsic mucosal immune system and anticancer pathways, and indirect mechanisms involving inhibition of pathogen

growth and breakdown of biofilms commonly associated with vaginal pathogen overgrowth. In-vitro studies have shown the antiproliferative and cytotoxic effects of *Lactobacillus* on cervical cancer cell lines.[77]

Both oral and vaginally administered probiotics have been found to colonise the human vagina. Most of the probiotic preparations used in the included studies were oral. Not all types of *Lactobacillus* probiotics can persistently establish themselves in the vagina; however, as highlighted by Gardiner and colleagues,[78] *L rhamnosus* GR-1 was more capable of persisting than strain GG. The earlier commercial probiotics aimed at improving gynaecological health contained various strains of *L rhamnosus* and *L reuteri*. However, considering the extensive data linking *L crispatus* to various health states, the interest in developing probiotic preparations containing this species has increased. Antibiotics are the only drugs routinely used for vaginal microbiota manipulation in clinical practice; the drugs most frequently used for bacterial vaginosis are clindamycin and metronidazole. Although the initial cure rate with these drugs is good, the associated recurrence rates are high. This approach can reduce populations of pathogenic anaerobes but is non-targeted and does not directly support *Lactobacillus* repopulation, which could be achieved through combination treatment involving both antibiotics and probiotics. Several studies have revealed that the combination treatment approach might be more effective than using antibiotics alone; however, appropriately designed studies, with an adequate sample size, are required for confirmation.[38] Furthermore, the combination of antibiotics and probiotic or prebiotic preparations has not been investigated in the context of gynaecological cancer prevention.

The currently included studies related to probiotics and prebiotics in gynaecological cancers have focused on altering the vaginal microbiota for clearance of HPV infection and cervical pre-invasive disease; none of the studies have explored other gynaecological malignancies. Although some results were promising, the studies generally had a small sample size, had varying designs, and did not include a placebo-treated group except for one study, by Di Pierro and colleagues,[51] which was the only study to evaluate the composition of the vaginal microbiota before and after probiotic administration. They showed that oral administration of *L crispatus* M247 resulted in 94% of participants having a *L crispatus*-dominant vaginal microbiota after treatment, although whether this effect was due to colonisation of the specific exogenous probiotic strain or endogenous *L crispatus* was not reported and the long-term effect of this treatment on the microbiome remains unknown. Although several types of *Lactobacillus* probiotics disappear shortly after cessation of use (within 4–6 months in some studies),[79] *L crispatus* CTV-05 (Lactin-V) persisted in 48% of users for up to 13 weeks after cessation of use in a trial demonstrating its efficacy in reducing the recurrence of bacterial vaginosis.[80] This preparation has not been investigated in relation to gynaecological cancer prevention but deserves consideration. None of the existing studies related to probiotic use in gynaecological precancer report on long-term outcomes, and whether long-term usage of probiotics is required remains unclear. Heterogeneity exists in terms of the type of probiotic used, data to inform dosing and duration of treatment are scarce, and mechanistic insights into how oral preparations might affect the vaginal microbiota are absent. These data indicate that not all *Lactobacillus* spp are equal in their ability to modulate the vaginal microbiome and highlight the importance of selecting an appropriate species and strain for treatment. Simply recommending a *Lactobacillus*-containing probiotic is thus insufficient, and further research is warranted to identify the optimal preparation.

Given the heterogeneity in terms of study design, duration of treatment, and preparation, performing a meta-analysis of the included studies was not possible, which is a limitation of this work. Additionally, many of the included studies involving prebiotics, probiotics, and other supplements reported cytological clearance and colposcopic appearance as primary outcomes, which can be subjective and are known to be associated with a high variation in sensitivity and specificity.[81] Furthermore, most studies do not provide information on whether the pathologists or colposcopists were masked to patient data or treatment groups, which would be required to draw more robust conclusions.

A continuum appears to exist between the composition of the vaginal microbiota and that of the upper FGT;[28–30] however, we have no evidence that manipulation of the vaginal microbiota can help to modify the composition of other FGT compartments. The probable interplay between the gut and FGT microbiota is unclear, and the role of the gut microbiota in gynaecological cancers also warrants further investigation. The gut microbiota composition might influence the FGT microbiota directly or indirectly through its ability to modulate circulating oestrogen levels. Oestrogens are known to influence the FGT microbiome composition,[82] which might aid in the development of oestrogen-driven type I endometrial cancers.[83] The gut microbiota might also influence the peritoneal microbiota, which should be investigated in relation to epithelial ovarian cancer. The role of confounding factors, such as diet, smoking, use of exogenous hormones, menopause status, and obesity, which might alter the gut and FGT microbiota structure, should also be considered in future studies.

Understanding the interplay between the FGT microbiome and disease can drive the development of predictive diagnostics and more targeted prevention techniques for individualised care.[84,85] After identifying the biomarkers of disease or disease progression, the development of rapid microbiome-based phenotyping tests for clinical risk stratification could help to identify who would benefit most from treatment and who could adopt a watch-and-wait policy. Specific microbiome

Search strategy and selection criteria

We searched PubMed, Google Scholar, ClinicalTrials.gov, WHO.int, and Web of Science for literature, trial registrations, and reports without restrictions on language. A combination of the keywords "microbiome", "microbiota", "flora", "cervical", "vulva", "vulval", "vulvar", "ovarian", "ovary", "uterus", "uterine", "endometrial", "endometrium", "vagina", "vaginal", "intraepithelial neoplasia", "squamous intraepithelial lesion", "precancer", "carcinoma", "cancer", "probiotic", "prebiotic", and "supplement" were used in the search string to select relevant studies published between Jan 1, 2000, and May 18, 2023. We included human studies that used next-generation sequencing to describe the microbiota in cervical, vulvar, vaginal, endometrial, or ovarian precancer or cancer with a control or comparator group. We further included studies reporting the use of prebiotic or probiotic products, or non-clinician prescribed supplements in people with these conditions. Studies that did not meet these inclusion criteria were excluded. Of the 25 315 references retrieved, 105 eligible studies were included.

signatures might also respond differently to different probiotic or prebiotic regimes, providing an opportunity to develop more personalised therapeutics.

Besides the studies on prebiotics and probiotics, we included 17 studies investigating the efficacy of over-the-counter supplements and treatments that are available without a clinician's prescription. Although there is no indication of these agents having any effect on vaginal microbiota composition, these studies were included in the current work to highlight the number of preparations available to people claiming an effect. The results show a high degree of variability and, although some compounds are reported to have a positive effect, the studies generally had small sample sizes and require replication in a larger population before the clinical value of the compounds can be substantiated.

Women with HPV and cervical disease as well as those who are or perceive themselves to be at risk of other gynaecological malignancies can be highly vulnerable to incompletely substantiated medical and scientific claims, which might prompt them to spend large amounts of money on a treatment that might not be beneficial. Although we do not have evidence of physical harm caused by the currently available probiotic preparations, we do not have good-quality evidence to support their use. The European Medicines Agency and US Food and Drug Administration now include probiotics in their list of compounds that require human drug approval when health claims are made, which has substantially changed the commercialisation of probiotics, as any marketed health benefits must now be backed by scientific validation. This change might encourage the pharmaceutical industry to fund high-quality research aimed at substantiating such claims. Currently, we have insufficient evidence to support the recommendation of probiotics, prebiotics, or other over-the-counter supplements for the prevention of gynaecological cancers. We welcome studies that further explore the interplay between the microbiota, host and exogenous factors, and heterogeneity of microbiota composition and disease outcomes between individuals. Rigorous research in these areas could lead to the development of novel therapeutics, allowing for a more personalised approach to treatment and prevention of gynaecological cancers.

Contributors

MK and MG conceptualised the manuscript. AM, MG, and MK contributed to the design. AM acquired and collated the data, with help from NB, LBE, SB, NT, and TB. AM drafted the manuscript. All authors revised the manuscript critically for important intellectual content and approved the final version.

Declaration of interests

PV-B has received honoraria and funding for travel from Seegene, Merck, Medinova, and Gedeon Richter, unrelated to this work. JS has received funding from GSK, AllergoSan, Lilly, Oncoinvent, MSD, Eisei, AstraZeneca, Clovis, PharmaMar, Seagen, Roche, and Novocure in various respects unrelated to this work and is on the advisory board for ENGAGE, ESGO, ENGIT, NOGGO, PARSGO, and AGO. MK has received funding from MSD, Hologic, and Inovio in various respects unrelated to this work. All other authors declare no competing interests.

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