THE MICROBIOME-CANCER NEXUS: EXPLORING FEMALE REPRODUCTIVE TRACT DYSBIOSIS IN GYNECOLOGICAL MALIGNANCIES

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A thesis submitted to the Department of Mathematics and Natural Sciences in partial fulfilment of the requirements for the Bachelor of Science in Microbiology

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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I/We have acknowledged all main sources of help.

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Approval

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Abstract

A specific microbiome is maintained to sustain equilibrium and good reproductive health in females. Unlike the uterus, fallopian tubes, and ovaries, which may possess a low-biomass microbiome comprising a diverse array of microorganisms, the vaginal and cervical microenvironment of the majority of reproductive women is predominantly characterized by Lactobacillus species, which confer advantages to the host through symbiotic interactions. Even when the microbiota's equilibrium is upset, illnesses like cancer may be impacted by the changed immunological and metabolic signals. Gynecological malignancies may develop as a result of these modifications to the pathophysiological axis. According to recent data, gynecological tract dysbiosis, or disturbance of microbiota homeostasis, can hasten the development and spread of a number of gynecological neoplasms, including ovarian, cervical, and endometrial malignancies. Prognosis, diagnosis, prevention, and the creation of novel therapies all depend on an understanding of the connection between microbiota and gynecological cancer. This study aimed to provide an overview of the current body of information and understanding on female reproductive tract dysbiosis in gynecological cancer.

Keywords: cervical cancer; dysbiosis; endometrial cancer; microbiome; ovarian cancer; vaginal cancer; vulvar cancer

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List of Acronyms

BV	Bacterial Vaginosis
ctDNA	Circulating tumor DNA
DNA	Deoxy ribonucleic acid
FMT	Fecal Microbiota Transplantation
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HSIL	High-Grade Squamous Intraepithelial Lesion
H2O2	Hydrogen peroxide
LPS	Lipopolysaccharide
MRI	Magnetic Resonance Imaging
MSI	Mass Spectrometry Imaging
Pap test	Papanicolaou smear test
PCOS	Polycystic ovary syndrome
RNA	Ribonucleic acid
VMT	Vaginal Microbiota Transplantation
VSCC	Vulvar Squamous Cell Carcinoma

1 Introduction

The impact of gynecological malignancies on reproductive health is enormous (Chi-Yuan & Kuo-Yen, 2024). Key causes of cancer development, in general, include environmental elements and genetic predispositions. However, recent research indicates that microbial populations within the human body plays a critical role in the pathophysiology of cancers (Kyrgiou & Moscicki, 2022). Over the last decade, gut microbiomes have been intensively investigated for its impact on immunological control, inflammation, and metabolism in the host- all of which are crucial for cancer development (Siddiqui, 2022). The microbiota of the female reproductive system has recently received increased interest. It is suggested that the dysbiosis of the se microbiota plays a role in the development and progression of gynecological cancers, which include cervical, endometrial, ovarian, vaginal and vulvar cancers (Castanheira, 2021). However, the precise processes by which microbial imbalances contribute to the development of gynaecological tumors are not yet fully understood (Bowden S. J., 2023).

The human microbiome, a complex ecosystem comprising bacteria, fungi, viruses, and archaea, is essential for maintaining homeostasis (Siddiqui, 2022). *Lactobacillus* species usually predominate in the vaginal microbiome of the female reproductive system, producing lactic acid, hydrogen peroxide, and bacteriocins to provide a protective environment for the host (Joana Castro, 2013); (Kyrgiou & Moscicki, 2022). However, microbial dysbiosis—characterized by a shift from a *Lactobacillus*-dominant environment to one enriched with anaerobic bacteria—has been associated with chronic inflammation, immune dysregulation, and increased susceptibility to infections such as human papillomavirus (HPV), a well-established driver of cervical cancer (Castanheira, 2021). Similarly, in endometrial and ovarian cancers, changes in both the local and gut microbiota have been reported in estrogen metabolism, inflammation, and immune modulation (Colbert L. E., 2023). The products of gut microbiota, mainly the estrobolome, appear to play a critical role in regulating circulating estrogen levels, which may have downstream effects on hormone-driven gynecological cancers (Bowden S. J., 2023). Despite the increasing body of literature highlighting these associations, a comprehensive understanding of how gut and reproductive tract microbiota contribute to gynecological carcinogenesis remains elusive (Siddiqui, 2022).

2 Scope of the Study

This study was motivated by the need to gain insight into the most recent studies encompassing the role of the microbiome of the female reproductive tract in the context of gynecological cancers. A broad range of peer-reviewed original articles, and systematic reviews have been thoroughly studied to achieve this aim. The findings from these sources highlight the intricate connection between cancer and the microbiome (Castanheira, 2021); (Colbert L. E., 2023); (Kyrgiou & Moscicki, 2022).

This study aims to bridge the gap between microbiome research and oncology by exploring how microbial balance affects the risk of cancer, disease progression, and treatment outcomes (Bowden S. J., 2023). This study also highlights the development achieved so far in cancer-care and patient well-being through microbiome-based therapies (Colbert L. E., 2023).

3 Female Reproductive Cancer

Cancers are characterized by the uncontrolled cell division, cell growth and spread of the abnormal cells (Roy & Saikia, 2016). The cancerous cells have the ability to invade the nearby cells and tissues and spread to distant parts of the body through different mediums like the bloodstream and the lymphatic systems (National Cancer Institute, 2021). This progression of the cell, if left unchecked, can cause severe systemic effects. Among the different causes, one of the root causes of cancer is in the genetic mutations or alterations in the cellular mechanisms of the body that is governed for cell division and programmed cell death commonly known as apoptosis (National Cancer Institute, 2021). These mutations in the cells disrupt the normal cellular processes and allow uncontrollable cell growth and evades cell death mechanisms (National Cancer Institute, 2021). The development of cancerous cells is often multifactorial; it arises from the complex interplay of the environmental exposures, choices in the lifestyle, and the hereditary predispositions of individuals. Carcinogenic elements from ultraviolet radiation, tobacco smoke, and the various chemicals contribute to the risk of cancer significantly, while genetic predispositions like the mutations of BRCA play a role in familial cancer syndromes (National Cancer Institute, 2021). Lifestyle factors of an individual which include diet, physical activity, and the reproductive history, influence the susceptibility of the cancer (National Cancer Institute, 2021).

Among the various cancers present, the reproductive system cancers stand out as one of the major concerns for women's health. The malignancies, which develop in the various parts of the reproductive organs and female genitalia act as a significant burden globally. Female reproductive cancers include the cancer of the cervix, endometrium, ovary, vagina, and the vulva (Weiderpass & Labrèche, 2012). Due to their late discovery or diagnosis, vaginal and vulvar cancers are still relatively uncommon but just as worrying as cervical, endometrial, and ovarian cancers (Weirderpass & Labréche, 2012). The human papillomavirus (HPV) infection is the main cause of cervical cancer. One of the main causes of mortality for women in lower- and middle-income nations is cervical cancer. Obesity and hormone imbalances are frequently linked to endometrial cancer. In developed nations, endometrial cancer, often known as gynecological cancer, is the most commonly diagnosed malignancy. Ovarian cancer is a leading cause of death for women because of its modest signs, which often lead to its detection at an advanced stage. The impact of these cancers not only limits physical health, but it also affects the mental well-being, female fertility, and the quality of life. With the blessings of

advanced screening tools, various vaccination programs (e.g., HPV vaccine), and the improved clinical treatments, efforts are being made in reducing the burden of reproductive cancers. However, in the underprivileged population the disparities in access to healthcare services, awareness for the disease, and the early detection programs continue to pose threats. Addressing female reproductive cancers needs a comprehensive approach, prevention, early detection, impartial access to treatment, and ongoing research on diagnostic and therapeutic strategies. Prioritizing the accurate approach may significantly alleviate the global burden of these cancers, improving the female health outcomes and the quality of life for numerous women across the world (Weirderpass & Labréche, 2012).

Gynecological cancers are classified into different categories which include cervical cancer, endometrial cancer, ovarian cancer, vaginal and vulvar cancer.

3.1 Cervical Cancer

Cervical cancer is primarily caused by human papillomavirus (HPV) infection; high-risk HPV strains, such as HPV-16 and HPV-18, are more likely to cause cervical cancer and account for the majority of cases. Frequent infections with these viruses lead to the changes of the cell's regulation cycle via E6 and E7 oncoproteins, which suppress p53 and RB eventually it progresses to cancer (Medina-Gutiérrez, 2022). E6 is known to hinder the work of tumor suppressor p53 which generally prevents the growth of damaged cells, abnormal cells survive after p53 is blocked by E6. E7 is known to hinder the work of another tumor suppressor called Rb, which regulates cell division therefore the inactivation of Rb leads to uncontrolled cell division (Zhang et al., 2017).

3.2 Endometrial (Uterine) Cancer

There are no specific microorganisms that are directly linked to endometrial cancer, its risks may be influenced by alterations in the vaginal microbiome. Imbalances due to microbes can contribute to an inflammatory environment where inflammation increases, which affects the endometrial health (Stabile, 2024).

3.3 Ovarian Cancer

For ovarian cancers the association or link between the pathogenic microorganisms and development of ovarian cancer is not well-established. Reproductive tract infections have chronically inflamed the tract that may contribute to the carcinogenesis of the ovary; however, the definitive links are lacking (Konstantinopoulos, 2022).

3.4 Vaginal Cancer

The chances of high-risk infections caused by Human papillomavirus (HPV) are also significant risk factors for vaginal cancer, it can also potentially lead to lesions of the pancreas that can develop to cancer if untreated (Shi, 2023). Vaginal cancer is a rare malignancy, accounting for about 3-5% of all gynecological cancer in economically developed nations (Wahid et al., 2022). Causative factors for cancer are not identified yet (Canavan et al., 2002).

3.5 Vulvar Cancer

About 3,200 cases and 800 fatalities of vulvar cancer occurred in the United States in 1998, making it a relatively uncommon malignancy that accounts for 3–5% of female genital tract cancers. Squamous cell carcinomas, which make up around 90% of vulvar cancers, often have a favorable prognosis if they are identified early by biopsy of suspicious lesions. There are two different pathogenic pathways: an HPV-independent pathway that is more prevalent in older women and is linked to chronic inflammatory conditions like lichen sclerosus that result in differentiated VIN, and an HPV-associated pathway that affects younger women by progressing from vulvar intraepithelial neoplasia (VIN) and is frequently linked to high-risk HPV types like HPV-16, -18, and -33. Women under 50 have shown an upsurge in VIN and VIN-related invasive malignancies over the last ten years, highlighting the significance of early identification and conservative treatment for better results.(Canavan et al., 2002).

4 Epidemiology

The study of all the variables that contribute to the occurrence of diseases and illnesses is known as epidemiology. The research aspect of epidemiology helps us determine how many individuals have a disease or problem, whether those numbers are changing, and how those numbers impact the economy or society (What is epidemiology?, 2011). Human communication epidemiology is a fascinating and demanding area. Self-report—the responses given by research participants—provides epidemiologists with a large portion of their data. Additionally, a lot of epidemiological estimations attempt to ascertain how the population afflicted by a condition evolves over time. However, estimations are more challenging since the definition of a condition also tends to evolve with time. The optimal approach to quantify or characterize a certain condition may not be agreed upon by scientists working in the same field at the same time (What is epidemiology?, 2011).

4.1 Cervical Cancer

With an estimation of 660,000 new cases and death cases reaching to 350,000 only in the year 2022 making cervical cancer as one of the most common cancers among women. Ninety-four of all these deaths are reported in countries with low-income and middle-income, highlighting the discrepancy in the access of healthcare (WHO, 2024). The estimation of 13,820 new cases of invasive cervical cancer and 4,360 deaths has been reported in the United States in 2024 (American Cancer Society, 2024). Incidence of cervical cancer is common among women in the age group of 35–44 years (American Cancer Society, 2024).

The effective screening programs and the HPV vaccination have significantly reduced the rates of incidence and mortality of cervical cancers with proper diagnoses; it has fallen by over 50% between the years 1975 to 2010 (SEER, 2024). However, the burden of cervical cancer remains high in the lower resource settings, necessitating the global health initiatives to improve preventive care and accessibility (WHO, 2024).

4.2 Endometrial Cancer

The most prevalent gynecologic cancer that develops in the lining of the uterus in women from industrialized nations is endometrial cancer. In 2024, the American Cancer Society projected that there would be 13,250 fatalities and 67,880 new cases in the US (ACS, 2024). About

420,368 new cases were reported worldwide in 2022, making it the sixth most prevalent cancer in women (WCRF, 2024). The incidence of endometrial cancer is rising among racial and ethnic minorities (Liu, 2023). The majority of cases are diagnosed in postmenopausal women, whose median age is 63. Obesity can promote endometrial proliferation due to increased estrogen levels making it a significant risk factor **(EGRP/DCCPS/NCI/NIH, 2024).** The other risk factors include diabetes, polycystic ovary syndrome (PCOS), and genetic susceptibility, such as Lynch syndrome (Jiang, 2021). The early detection of the cancer is very crucial, as the localized endometrial cancer has a five-year relative survival rate of 94.8% (SEER, 2024). However, with advanced stages the survival rates decrease swiftly. The recent studies highlight the need for improved and advanced screening due to the issues found in diagnostic accuracy of the cancer among different populations. Endometrial cancer poses a public health challenge for more developed regions. The global burden can be reduced by addressing the modifiable risk factors, enhancement of the early detection of cancer, and ensuring all equitable healthcare access are the crucial steps toward success.

4.3 Ovarian Cancer

Ovarian cancer, one of the least common cancers, however, is the most lethal gynecologic cancer because of its late diagnosis. It accounts for approximately 3% of all cancers in women but ranks fifth in deaths among women due to cancer (Wijayabahu, 2024). The risk factors of ovarian cancers include the genetic mutations of (BRCA1/BRCA2), also the individual's family history including the infertility treatments. The survival rate (five-year) has significantly improved over the time due to the advancement in the technology of targeted therapies, but issues arise due to the outcomes of the geographic factors and socioeconomic factors (Barczyński, 2023).

4.4 Vaginal Cancer

Vaginal cancer is one of the rarest female reproductive cancers, which makes less than 2% of all the gynecological cancers globally. The infection caused by Human papillomavirus (HPV) is one of the major risk factors of vaginal cancer, marking over 70% of cell carcinomas of the vagina (WHO, 2024). Older women with a median age of 67 years are most of the patients. The rate of survival for vaginal cancer is comparatively higher if diagnosed at an earlier stage,

however the screening methods for vaginal cancers are limited compared to cervical cancer (Chen S. L., 2021).

4.5 Vulvar Cancer

In older women, vulvar non-neoplastic epithelial diseases (VNED) that progress to cellular atypia and cancer are connected to vulvar cancer, while another is linked to HPV infection, which causes VIN and ultimately carcinoma. Though 15% of instances occur in women under 40, and the number of younger women affected has significantly increased over the past 20 years, it primarily affects women 65 to 75. Over a 20-year period, the frequency increased from 2% to 21% in women under 50.

Eighty percent of untreated instances develop into invasive illness, and the majority of younger-onset malignancies start from warty or basaloid VIN. By the age of 75, the incidence peaks at 20 per 100,000 women, with around 30% of patients being 70 years of age or older. This translates to a 0.3% lifetime chance of getting vulvar cancer and a 0.1% chance of dying from it. Although disorders including obesity, diabetes, and hypertension can co-occur in as many as 25% of patients, they are not independent risk factors, and because of their decreasing occurrence, previous links with granulomatous diseases or syphilis are now seen as implausible. (Canavan et al., 2002)

5 Microbiota of the Female Reproductive Tract

The female reproductive tract's microbiota plays a role in controlling reproductive health, and *Lactobacillus* species are prevalent in the cervix, vagina, and endometrium. These species aid in pH management and the prevention of harmful infections. Numerous gynecological malignancies, including cervical, endometrial, ovarian, and vaginal cancers, have been linked to dysbiosis, or microbial imbalance, in which anaerobic bacteria, which induce chronic inflammation and carcinogenesis, proliferate and *Lactobacillus* decreases. It is well recognized that microbial diversity and immunological modulation are altered by hormonal fluctuations, HPV infections, and other external lifestyle choices, which in turn affect dysbiosis. Research has focused on the possibility of microbiota-based treatments, including probiotics, vaginal microbiota transplantation, and medications that target microbiomes, to restore microbial balance and reduce the risk of cancer. However, there are still significant obstacles to incorporating microbiome-based treatments into clinical practice, including regulatory obstacles, individual microbiome variability, and standardization of microbiome research methodologies.

Table 1: Types of cancer, causing bacteria, mechanism, pathophysiology and impact.

Cancer	Bacteria/ Organisms	Mechanism	Pathophysiology	Impact	Doi
Cervical Cancer	*Lactobacillus* (↓ in dysbiosis), *Gardnerella, Prevotella, Sneathia*	Decrease in *Lactobacillus* raises pH, allowing overgrowth of anaerobic bacteria; HPV infection disrupts tumor suppression	HPV E6 and E7 oncoproteins inactivate tumor suppressor genes (*p53*, *pRb*), leading to uncontrolled cell division and genomic instability	Increased risk of persistent HPV infection, chronic inflammation, and tumor formation	https://doi.org/10.3389/fmicb.2021.767931 https://doi.org/10.3390/diagnostics13050877 https://doi.org/10.1186/s13027-024-00590-7 https://doi.org/10.1128/jvi.78.21.11451-11460.2004 https://doi.org/10.1002/path.2192

Endometrial Cancer	*Lactobacillus* (↓ in dysbiosis), *Porphyromonas, Prevotella, Bacteroides, Fusobacterium*	Overgrowth of anaerobic bacteria produces pro-inflammatory molecules (LPS), promoting chronic inflammation	Inflammatory damage, immune dysregulation, and epithelial alterations contribute to carcinogenesis	Increased risk of endometrial cancer, hormone metabolism alterations, and immune suppression	https://doi.org/10.1038/s41467-017-00901-0 https://doi.org/10.1186/s13073-016-0368-y https://doi.org/10.3390/jpm11070659 https://doi.org/10.3390/diagnostics13050877 https://doi.org/10.3389/fcimb.2022.1059825
Ovarian Cancer	*Lactobacillus (↓ in dysbiosis), Chlamydia trachomatis*, gut microbiota imbalance	Chronic infections and inflammation, gut microbiota regulation of inflammatory pathways (Hedgehog signaling)	Inflammatory responses damage ovarian tissues, promoting carcinogenesis	Increased susceptibility to ovarian cancer, chronic inflammation, and immune modulation	https://doi.org/10.3390/pharmaceutics15030948 https://doi.org/10.1080/19490976.2023.2221093 https://doi.org/10.3390/diagnostics13050877 https://doi.org/10.2174/1871530322666220509034847 https://doi.org/10.1186/s10020-021-00295-2

Vaginal Cancer	*Lactobacillus (↓ in dysbiosis), Gardnerella vaginalis, Atopobium vaginae, Prevotella*	Reduction in Lactobacillus leads to increased pH, allowing overgrowth of anaerobic bacteria	Creates a pro-inflammatory environment, increasing risk of malignancy	Increased risk of bacterial vaginosis, chronic inflammation, and potential carcinogenesis	https://doi.org/10.3390/genes14040936
Vulvar Cancer	*Lactobacillus (↓ in dysbiosis), Finegoldia, Corynebacterium, Anaerococcus and Staphylococcus*	*Lactobacillus* and increased pH lead to microbial imbalance and inflammation; persistent HPV-16 infection disrupts tumor suppression via E6/E7 oncoproteins.	High-risk of HPV-16 infection: it integrates viral DNA into host cells, also promotes the expression of E6/E7 oncoproteins, which leads to inactivation of p53 and pRb, dysplasia, and malignant transformation.	Increased risk of chronic inflammation, immune evasion. Vulvar intraepithelial neoplasia and invasive squamous cell carcinoma can progress to.	https://doi.org/10.1186/s12967-023-04113-7 https://doi.org/10.3389/fmicb.2023.1264768

5.1 Microbiota of the Cervix

The cervix, the bottom portion of the female uterus, contains a distinct microbiota that is recognized to be essential to maintaining reproductive health. Similar to the vaginal microbiota, *Lactobacillus* species make up the majority of the cervical microbiome. *Lactobacillus crispatus*, *Lactobacillus gasseri, Lactobacillus jensenii*, and *Lactobacillus iners* are among the species of *Lactobacillus* that provide an acidic environment and suppress pathogenic organisms. However, certain unique characteristics are exhibited by the cervical microbiota compared to the vaginal microbiota for instance a higher proportion of *Proteobacteria* is found in the cervical microbiota (Zhang, 2021). Bacterial loads are lower in cervical microbiota however, according to studies cervical microbiota and vaginal microbiota tend to show similarities (Kyrgiou M. M., 2016). Additionally, various factors like the changes in the hormones, sexual activity and presence of any infection can influence the microbiota of the cervix. For instance, association of human papillomavirus (HPV) infection with various bacterial taxa have been made which statuses in cytologically normal women (Ritu, 2018).

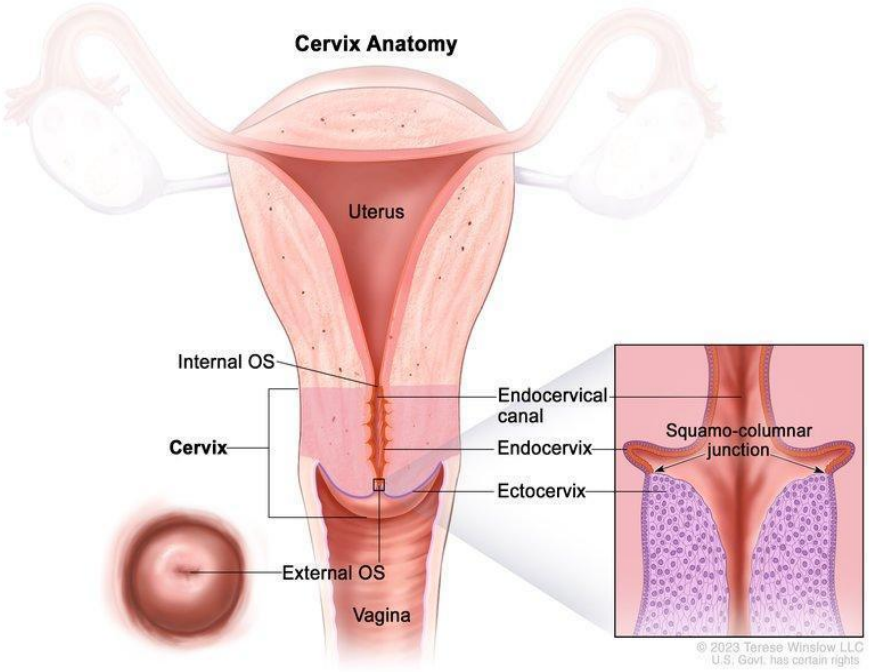

Figure 1: Cervix (Cervix Anatomy: Image Details - NCI Visuals Online, n.d.)

A well-balanced cervical microbiota is highly essential for the reproductive health of females, as disruptions in the balance can potentially lead to critical conditions like the cervicitis and it may even influence the progression of cervical intraepithelial neoplasia. Ongoing research on

reproductive microbiota continues to explore the various complex interactions of the cervical microbiota and their health implications on women.

5.2 Microbiota of the Endometrium

The uterine lining is called the endometrium. For a long time, it was thought to be a sterile environment, but new technology has revealed that there is a distinct microbiota there. It is well recognized that this microbiota is important for preserving fertility and the health of the female uterus. Different *Lactobacillus* species are known to dominate the vaginal microbiota, but the endometrial microbiome is distinct. It exhibits a lower diversity and abundance of microbes, it has instead a comprising mix of *Lactobacillus spp., Bifidobacterium, Prevotella, Gardnerella, and Atopobium* species. The dominance of Lactobacillus is often linked with a healthy uterine environment for their ability to produce lactic acid, lactic acid tends to lower pH and inhibits the colonization of pathogens, the *Lactobacillus* species are particularly *Lactobacillus iners and Lactobacillus crispatus*, (Chen C. S., 2017). According to studies, the endometrial microbiota plays an important role in the regulation of the immune system and the influence of implantation in the uterus resulting in successful pregnancy outcomes (Moreno, 2016). Imbalances in the microbiota can lead to conditions like chronic endometritis, infertility and recurrent implantation failures and this could be due to the decrease in *Lactobacilli* or an increase in the pathogenic microbes like *Gardnerella vaginalis* or *Escherichia coli*. The endometrium's microbial composition is influenced by hormonal changes, blood flow in menstruation, migration of the microbes from adjacent reproductive sites especially the vagina.

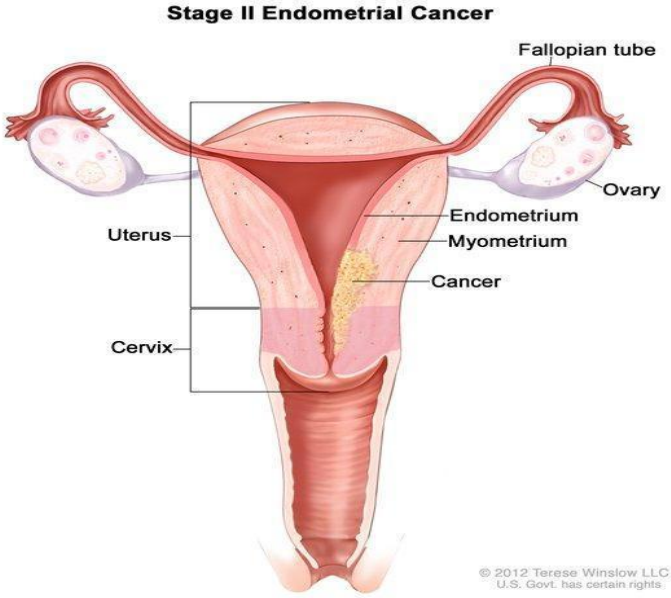

Figure 2: Endometrium (Endometrial Cancer Stage II: Image Details - NCI Visuals Online, n.d.)

5.3 Microbiota of the Ovary

The upper female reproductive tract was considered to have a sterile environment; however, recent studies have different opinions on this. Using advanced molecular techniques in various studies bacterial DNA has been detected in ovarian tissues, suggesting the presence of a unique microbial community (Brewster, 2022). The ovarian microbiota's composition has appeared to be different from that of other sites of the reproductive tract. The upper reproductive part is discovered to be abundant with Proteobacteria, including the ovaries, followed by *Firmicutes, Bacteroidetes,* and *Actinobacteria* (Cazzaniga, 2022).

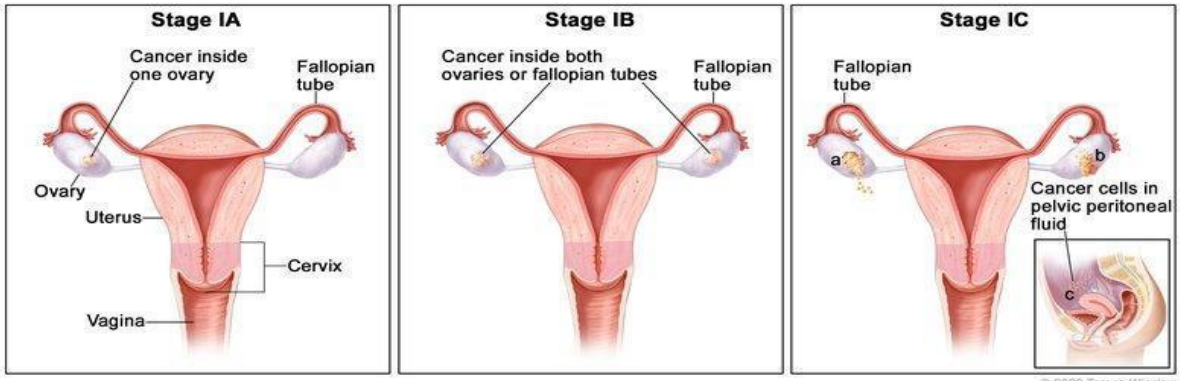

Figure 3: Ovary (Ovarian Cancer Stage I: Image Details - NCI Visuals Online, n.d.)

5.4 Microbiota of the Vagina

The vaginal microbiota plays an important role in the maintenance of the female reproductive health, its composition is influenced by different factors which include female life stages, hormonal changes and the external behaviors. A child born vaginally receives its initial microbiota from the mother's vaginal microbiota and skin microbiota, subsequently more colonization occurs from the oral flora and breastmilk, which is rich in *Lactobacilli* (Martin R, 2003). Before menarche in females, the vaginal microbiota is dominated by the microbiomes of skin and gut, however in the years followed by menstruation it transitions and is dominated by the Lactobacillus rich ecosystem. It occurs due to the increased levels of estrogen and progesterone; the hormones estrogen and progesterone stimulate the production of glycogen which Lactobacilli successfully metabolizes into lactic acid which allows it to protect against pathogens by maintaining the vagina's acidic pH of 3.8-4.4. There are a number of *Lactobacillus* species, however the most common species include *Lactobacillus crispatus*, *L.*

gasseri, L. jensenii, and L. iners., They are known to produce lactic acid, bacteriocins, biosurfactants, and hydrogen peroxide (H_2O_2) which are known to inhibit pathogens in the vagina and it also prevent the bacterial vaginosis (BV) (Vasquez A, 2002). Despite over 120 *Lactobacillus* species described, 250 bacterial species are found in the vaginal microbiota according to the genomic studies, this includes the *Gardnerella, Streptococcus, Prevotella,* and others, the prevalence is influenced by the females ethnic and behavioral factors. For instance, non-Lactobacillus species are more prevalent in Hispanic and Black women, while in Asian women *L. crispatus* is common (Ravel J, 2011). The microbiota shows resilience; it restores the balance after disturbances from sexual activity or using tampons, still prolonged imbalances can lead to various critical conditions like BV or cytolytic vaginosis, these are characterized by dysuria and pruritus. To prevent infections, to reduce the risk of infection with HIV, and to protect against premature birth and to ascend infections, underscoring the importance of healthy vaginal microbiota is essential in reproductive health (Hoyme UB, 2010).

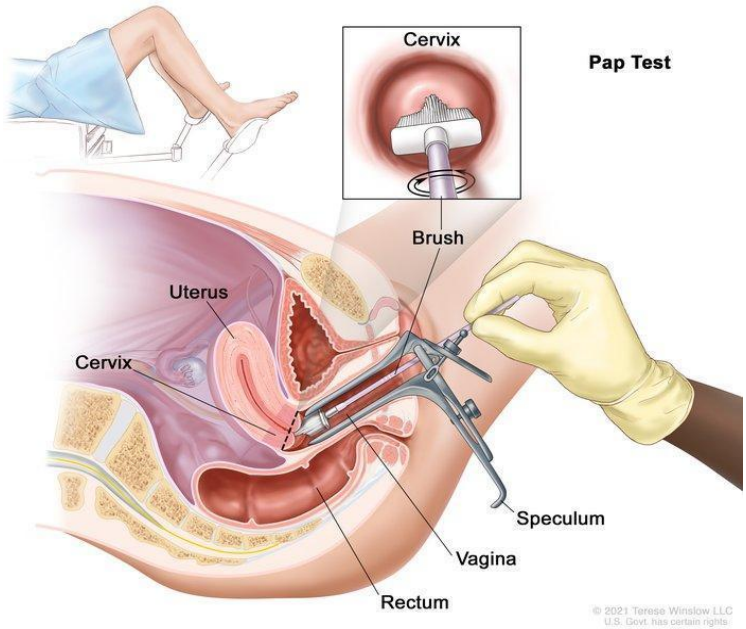

Figure 4: Vaginal opening (PAP Test: Image Details - NCI Visuals Online, n.d.)

5.5 Microbiota of the Vulva

The vulva's appearance is a vague concept that is seldom ever depicted in textbooks. Vulva is the external genitalia of the females (Sacher, 2015). The vulva is relatively abundant with five most abundant genus found in the inner vulva area, which includes the inner labia and the outer

labia. The abundant genera comprise *Finegoldia, Lactobacillus, Corynebacterium, Anaerococcus* and *Staphylococcus* (Vongsa et al., 2019).

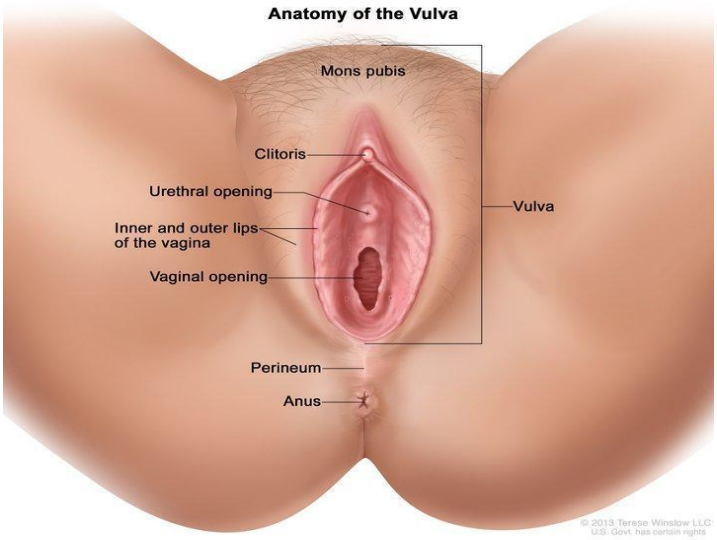

Figure 5: Vulva (Vulva Anatomy: Image Details - NCI Visuals Online, n.d.)

6 Symbiosis and Dysbiosis

The human microbiome is composed of a diverse range of microbial communities, these microbial communities play a pivotal role in maintaining health, which also includes the female reproductive tract. Symbiosis is the peaceful coexistence of microbial communities, whereas dysbiosis is an imbalance that develops in microbial communities. On the other hand, alterations that take place in microbial communities, referred to as dysbiosis, have been linked to numerous gynecological cancers. An overview of the symbiotic which is (healthy) and dysbiotic which is (imbalanced) of microbiomes associated with cervical, endometrial, ovarian, and vaginal cancers are discussed below.

6.1 Cervical Cancer

Symbiosis: In a healthy female, *Lactobacillus* species usually dominate the vaginal microbiome. *Lactobacillus* is known to create lactic acid, which keeps the pH below 4.5. *Lactobacillus* maintains this acidic environment, which promotes the cervical health of the female reproductive system by preventing the growth of other harmful microbes.

Dysbiosis: It is well known that *Lactobacillus* helps to keep the cervix and vagina at a pH that prevents the formation of harmful bacteria. On the other hand, the degree of *Lactobacillus* dominance is significantly reduced in cervical cancer, which results in a greater diversity of microorganisms. Anaerobic bacteria like *Gardnerella, Prevotella*, and *Sneathia* tend to proliferate more when the quantity of *Lactobacillus* fluctuates. According to Javadi et al. (2024), chronic human papillomavirus (HPV) infections, a significant risk factor for cervical cancer, have been related to elevated vaginal pH in females. Human papillomavirus (HPV) disrupts the tumor suppressive mechanism, which is a crucial factor in the development of cervical cancer in females. High-risk HPV strains include HPV-16 & HPV-18. The viral oncoproteins which play a central role in cervical cancer are E6 and E7. E6 tends to bind with the p53 protein and then later proceeds to degrade it, which leads to impairing the DNA repair and apoptosis, on the other hand E7 inactivates the retinoblastoma protein (pRb), the inactivation of pRb leads to an uncontrolled cell division (Javadi et al., 2024). Persistent HPV infection, facilitated by the integration of viral DNA into the host genome, results in the overexpression of the E6 and E7 oncoproteins, accumulation of mutations lastly the genomic instability (Javadi et al., 2024). Additionally, HPV also evades the immune system and it

induces chronic inflammation in the reproductive organ leading to a tumor-promoting environment (MüNger, 2004).

6.2 Endometrial (Uterine) Cancer

Symbiosis: The upper female reproductive tract including the endometrium, was traditionally considered sterile for a long time but recent research contradicts this traditional concept. However, recent studies suggest endometrium harbors a low-biomass microbiome, with *Lactobacillus* species which contributes to a balanced environment (Chen C. S., 2017).

Dysbiosis: In endometrial cancer, an increase in microbial diversity with a higher presence of anaerobes is observed. This imbalance in microbes may result in serious inflammatory processes and carcinogenesis within the endometrium. In dysbiosis related with endometrial cancer, various anaerobic bacteria have been considered to alter the microbiome. These include species of various anaerobes such as *Porphyromonas, Prevotella, Bacteroides,* and *Fusobacterium*. Lipopolysaccharides (LPS) and proinflammatory molecules are known to be produced by anaerobes, which can promote chronic inflammation, can damage DNA, and can lead to carcinogenesis. Studies have suggested that these anaerobic bacteria might influence hormonal metabolism in females, alter the immune responses, and epithelial integrity, creating a tumor-promoting microenvironment (Walther-António, 2016).

6.3 Ovarian Cancer

Symbiosis: The ovaries are organs which are part of the upper reproductive tract in the female, which generally has a low microbial presence; however, *Lactobacillus* species are present and are considered to be beneficial. In a healthy state, the ovarian microenvironment in females maintains a low-biomass microbiome which is influenced by the microbial migration from different tracts which includes the vaginal and gastrointestinal tracts. *Lactobacillus* species are well known for their protective role; it contributes to immune homeostasis by the production of lactic acid; the acidic environment suppresses the growth of pathogenic bacteria and causes inflammatory responses. This balanced environment of microbes supports tissue integrity, and it also tends to reduce the risk of malignancy. The ovarian microbiome remains to be one of the less studied parts than others in the reproductive tract microbiomes, its proper function prevents chronic inflammation and infections which could potentially promote cancer (Zhao, 2023).

Dysbiosis: According to research, ovarian cancer dysbiosis is associated with higher microbial diversity and lower *Lactobacillus* dominance levels. Notably, the risk of ovarian cancer is to be increased with the presence of bacteria such as *Chlamydia trachomatis*. Carcinogenesis is led by the contribution of chronic infections and the resulting inflammatory responses from it. Additionally, in the development of ovarian cancer the gut microbiota dysbiosis has been implicated, it occurs potentially via the regulation of inflammatory pathways like the Hedgehog signaling pathway (Hu, 2023). It is to be noted that the associations between microbial communities and ovarian cancer have been observed, the exact mechanisms and causative relationships for ovarian cancer remain as an area of active research.

6.4 Vaginal Cancer

Symbiosis: A *Lactobacillus* dominated vaginal microbiome maintains low acidic pH in the vagina which is caused by the *Lactobacillus* and it protects against unwanted pathogenic infections, which tends to support the vaginal health in females (Valeriano, 2024).

Dysbiosis: Studies on vaginal cancer is limited, but it is understood that a decrease in the level of *Lactobacillus* and an increase in the level of anaerobic bacteria like *Gardnerella vaginalis*, *Atopobium vaginae*, and *Prevotella* species can lead to severe conditions like bacterial vaginosis in females. Such dysbiosis tends to create a pro-inflammatory environment which can easily lead to carcinogenesis (News-Medical, 2023).

6.5 Vulvar Cancer

Symbiosis: A predominating *Lactobacillus* species colonizes the (inner labia) vulva it is known to produce lactic acid and maintains the acidic pH which inhibits the pathogenic microorganisms (Padmasana, 2023). *Finegoldia* also colonized the inner labia. The outer labia is like the regular skin and is known to host *Corynebacterium* and *Staphylococcus* (Sacher, 2015). The distinction of microbial colonization region reflects a functional adaptation to the local conditions of the vulva; it supports the integrity of the skin and mucosa and reduces the chances of infections and inflammation. A stable microbial environment like this may potentially act as a protective barrier against external irritants, opportunistic pathogens, even the malignant transformations, contributing to an overall vulvar health (Javadi et al., 2024).

Dysbiosis: This disturbance in the microbial state potentially compromises the protective barrier of the vulva, this then proceeds to create an environment which is more prone to chronic

inflammation, immune dysfunction, and also persistent HPV infection (Sacher, 2015). The higher risk strain of HPV better known as HPV-16 has stronger association with vulvar cancer more particularly in young women who have histories of genital warts, cervical dysplasia, or immunosuppression (Javadi, 2024). Squamous cell carcinomas comprise about 90% of vulvar cancers whereas, HPV-16 makes about 80–90% of HPV-positive vulvar cancers, continuous HPV infection in the light of vulvar dysbiosis might have an impact in oncogenesis (Wahid et al., 2021). Therefore, dysbiosis not only weakens mucosal defenses but it may also act as a contributing factor for the pathogenesis of vulvar malignancies, to be particular when it is coupled with other risk factors which could range from tobacco smoking to inflammatory vulvar conditions, and to prior experience of radiation exposure (Javadi et al., 2024).

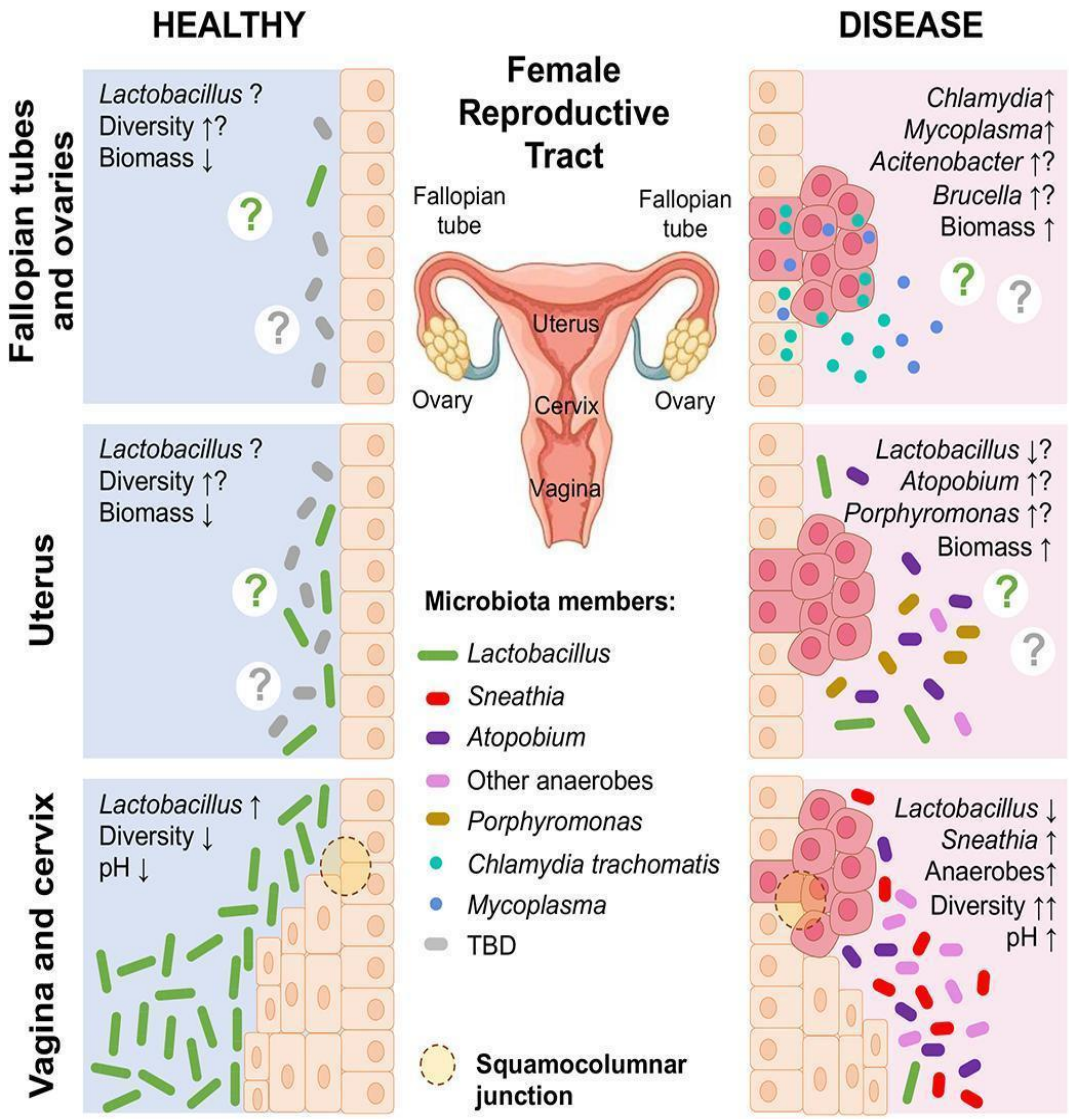

Figure 6: Symbiosis and Dysbiosis (Łaniewski et al., 2020)

7 Risk Factor of Dysbiosis and Protective Factors of Symbiosis

Numerous gynecological malignancies, including those of the cervix, endometrium, uterus, vagina, and ovary, have been connected to the female reproductive system. Below is a summary of the protective variables associated with symbiosis and the risk factors associated with dysbiosis for specific cancers, which are backed by several recent study findings.

7.1 Cervical Cancer

Dysbiosis - Risk Factors:

- **High-Risk of Human Papillomavirus (HPV) Infection:** Persistent infections with various strains of high-risk HPV is a well-studied risk factor supported by numerous research findings for cervical cancer. The vaginal microbiota's dysbiosis, caused by a reduced number of *Lactobacillus* species and increased number of anaerobic bacteria, can facilitate persistence of HPV and can gradually progress to cancer (Trifanescu O. G., 2023).
- **Reduced Lactobacillus Dominance:** A higher pH of vagina is caused by the decreased levels of *Lactobacillus* species, which proceeds to create an environment that is conducive to pathogenic bacteria and HPV infection (Trifanescu O. G., 2023).

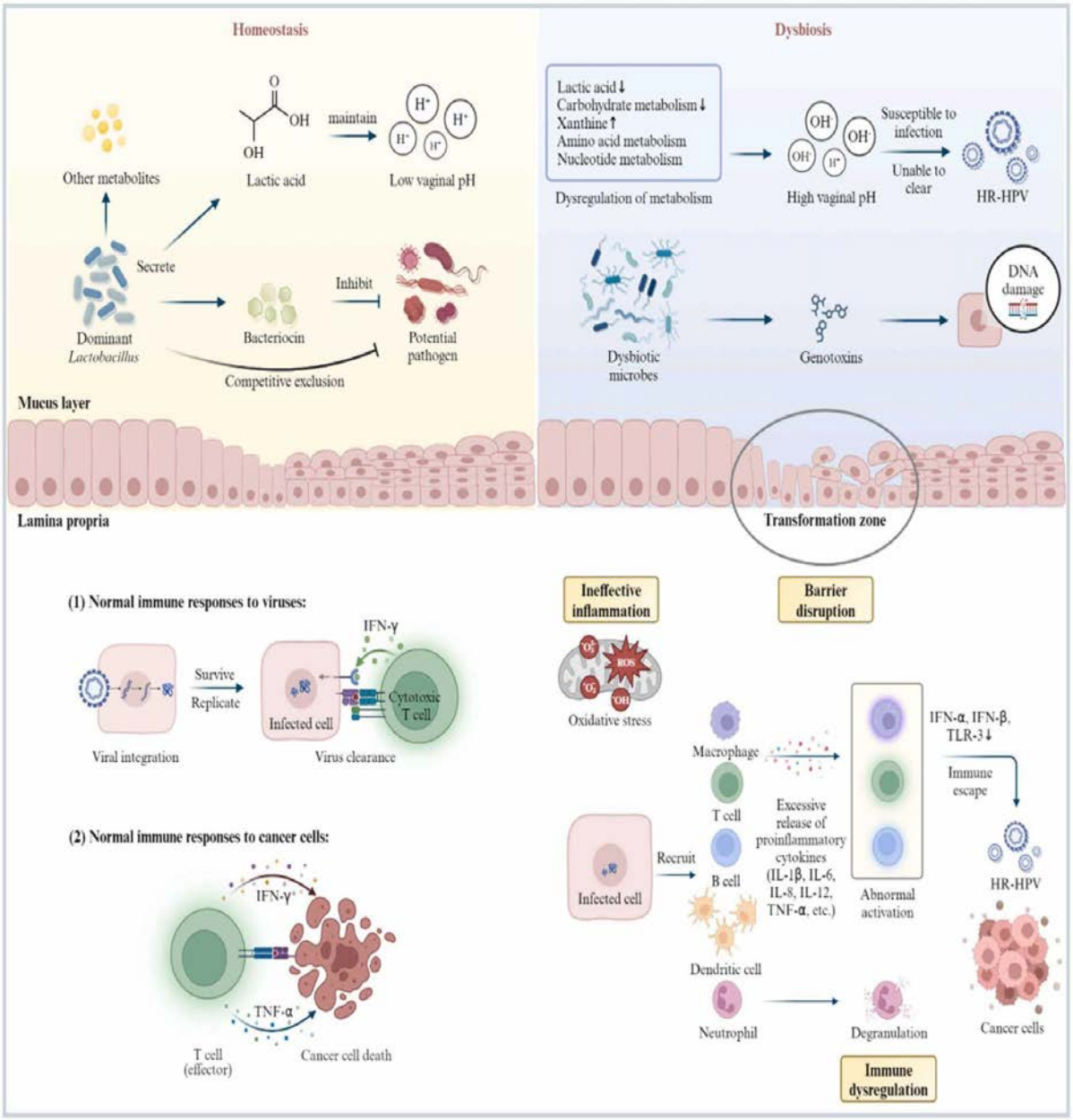

Figure 7: Dysbiosis of cervix (Huang et al., 2024)

Symbiosis - Protective Factors:

- ***Lactobacillus* Species:** Vaginal microbiota is dominated by *Lactobacillus* spp. which helps to maintain an acidic environment of the vagina, also inhibits the growth of pathogenic bacteria and tends to reduce HPV infection risk (Trifanescu O. G., 2023).

7.2 Endometrial (Uterine) Cancer

Dysbiosis - Risk Factors:

- **Higher Vaginal pH:** An increased pH level of the vagina has a correlation with higher risk of endometrial cancer, the pH rises due to a reduction in the number of *Lactobacillus* species and an overgrowth in the number of anaerobic bacteria (Boutriq, 2021).
- **Presence of Specific Bacteria:** The presence of bacteria such as *Atopobium vaginae* and *Porphyromonas* species has an association in the cases of endometrial cancer, potentially due to their ability in creating chronic inflammation and creating a dysregulation in the local immune (Boutriq, 2021).
- **Microbial Imbalance:** Dysbiosis in the uterine microbiome leads to persistent infections with microbes. In the uterus it is considered as a well-known risk factor for cancers (Trifanescu O. G., 2023).

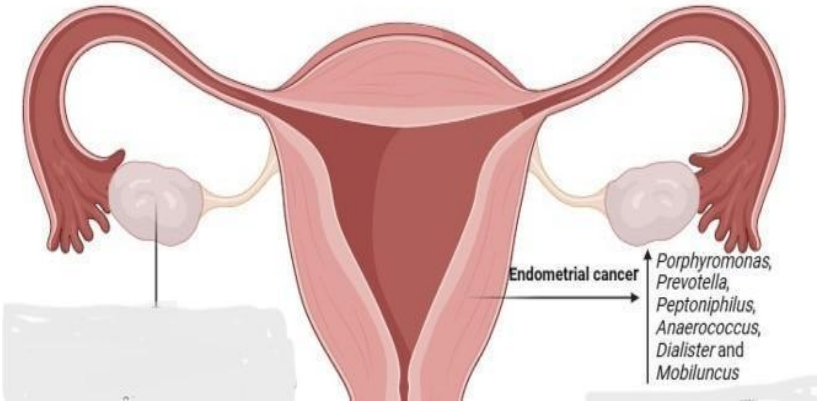

Figure 8: Dysbiosis of endometrium (Javadi et al., 2024)

Symbiosis - Protective Factors:

- **Balanced Microbiota:** Endometrium cancer can be prevented by maintaining a balanced microbiota which prevents chronic inflammations in the endometrium and tends to maintain immune homeostasis (Trifanescu O. G., 2023).
- **Healthy Microbiome of the Uterus:** A uterine microbiome generally supports the immune function and protects against any inflammatory processes that may contribute to the development of cancer (Trifanescu O. G., 2023).

7.3 Ovarian Cancer

Dysbiosis - Risk Factors:

- **Alteration in the Vaginal Microbiota:** Dysbiosis in the microbiota of ovary causes ovarian cancer (Trifanescu O. G., 2023).
- **Specific Bacteria's Presence:** *Proteobacteria*, *Brucella Acinetobacter* spp., and viruses like cytomegalovirus or HPV cause ovarian cancer if they are present in the ovarian microbiota (Trifanescu O. G., 2023).

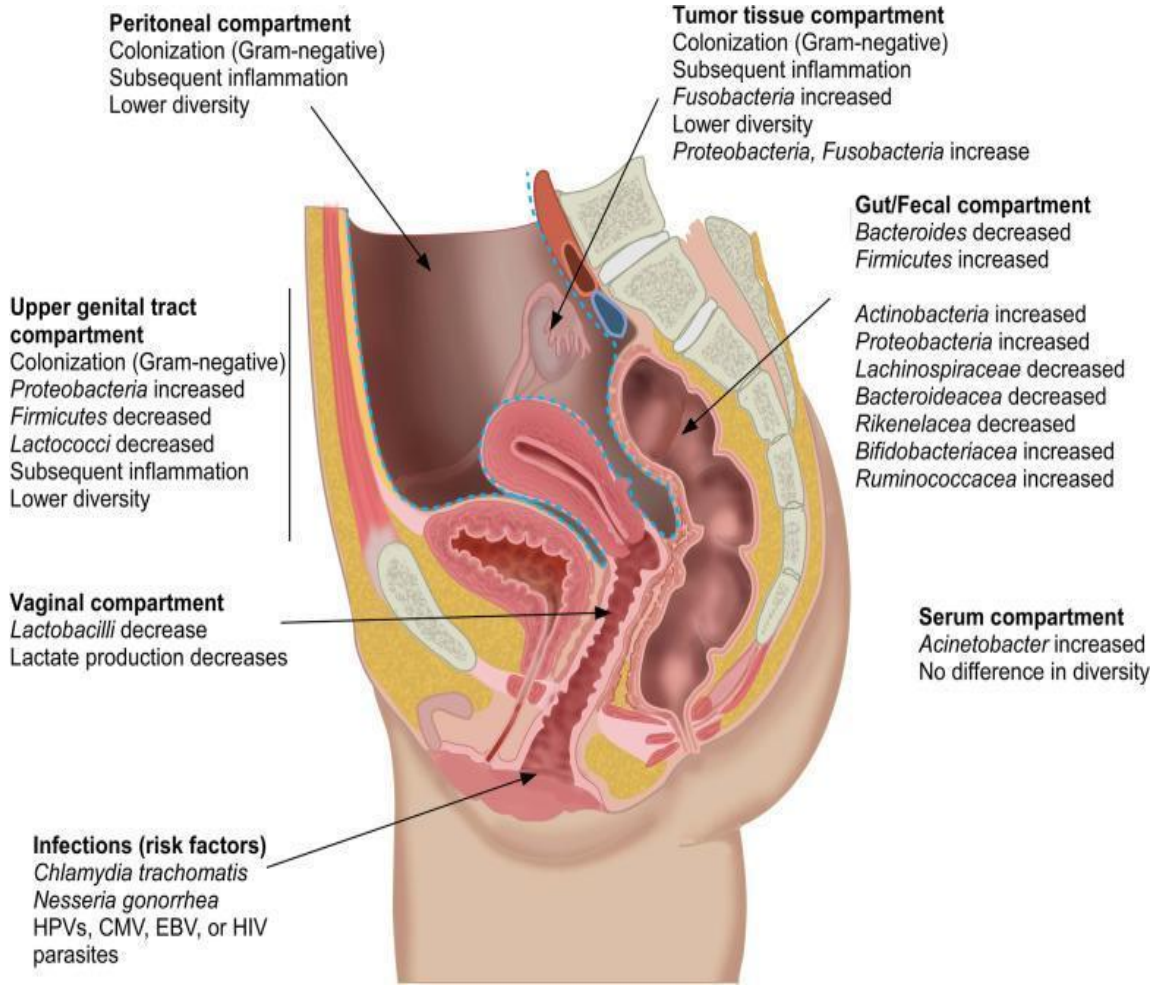

Figure 9: Dysbiosis of ovary (Sipos et al., 2021)

Symbiosis - Protective Factors:

- **Lactobacillus Species:** Vaginal microbiota is highly dominated by *Lactobacillus* species that have a protective role against ovarian cancer (Trifanescu O. G., 2023).

7.4 Vaginal Cancer

Dysbiosis - Risk Factors:

- **Imbalance of Microbes in the Vagina:** *Lactobacillus* and anaerobic bacteria creates an imbalance in the vaginal microbiota that causes persistent infections which leads to cancer (Trifanescu O. G., 2023).

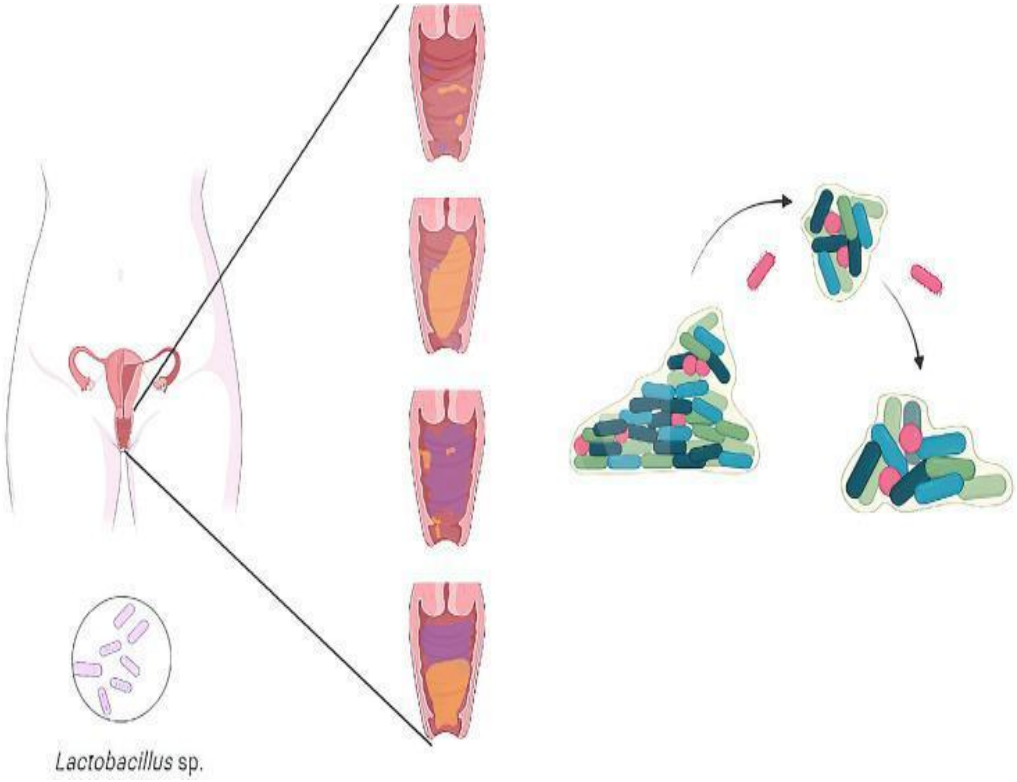

Figure 10: Dysbiosis of vagina (Machado et al., 2022)

Symbiosis - Protective Factors:

- **Lactobacillus Dominance:** Acid producing bacteria, *Lactobacillus*, maintains a lower pH in the vaginal microbiota and the acidity produces inhibits pathogenic microbes that reduces risk of cancer (Trifanescu O. G., 2023).

7.5 Vulvar Cancer

Dysbiosis – Risk Factors:

- **Microbial Diversity and Imbalance:** The vulvar microbiome is more diverse than the vaginal one. It includes bacteria that come from the skin, the gut, and the vaginal area (Pagan et al., 2021). In women with vulvar skin conditions, this diversity becomes even more noticeable. Some of the common bacteria found are *Prevotella spp.*, *Porphyromonas spp.*, and *Peptoniphilus spp.*. These bacteria are linked to inflammation, especially in women with lichen sclerosus. Over time, this kind of long-term inflammation may increase the chance of developing vulvar squamous cell carcinoma, especially in cases not linked to HPV (Pagan et al., 2021; Pagan et al., 2023).

- **Reduced Lactobacillus Dominance:** *Lactobacillus* species are not as common on the vulva as they are in the vagina. These bacteria help keep the area healthy by producing lactic acid and keeping the pH low. When there are fewer of them, harmful bacteria can grow more easily. This change may lead to irritation, infections, and even early changes in the skin that would later become cancerous, especially in women who are already at risk (Pagan et al., 2021; Javadi et al., 2024).

- **Specific Pathogen Presence:** Some bacteria have been found more often in women with vulvar diseases. These include *Staphylococcus aureus*, *Corynebacterium*, *Actinomyces*, and *Ezakiella*. These bacteria can disturb the immune balance of the skin and break down its protective barrier. This makes the skin more open to damage and disease (Pagan et al., 2021; Taylor et al., 2024).

  In some studies, women with more of these bacteria had worse symptoms of lichen sclerosus, such as pain and skin thinning (Taylor et al., 2024). Other bacteria like *Fusobacterium nucleatum* and *Pseudomonas aeruginosa* have been found inside vulvar cancer tumours. These microbes were linked to faster cancer growth and lower survival rates. This means the bacteria in the tumour may actually make the disease worse (Rustetska et al., 2023).

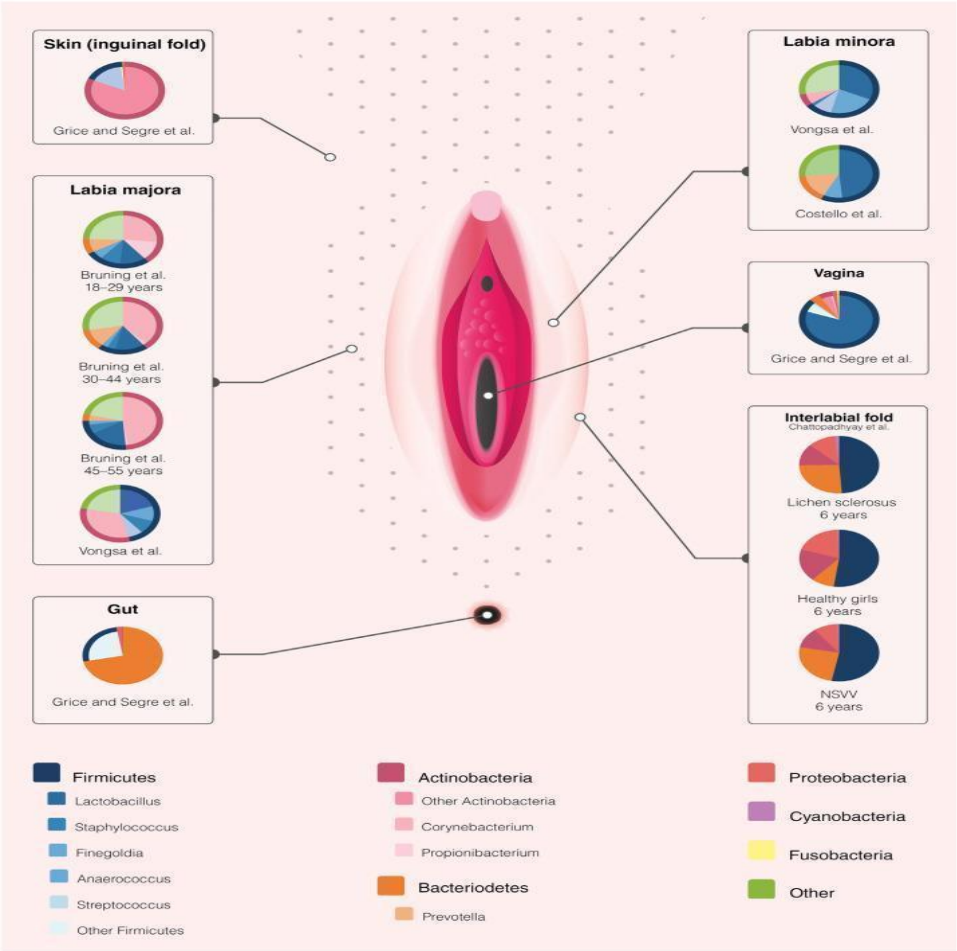

Figure 11: Microbiome of vulva (Pagan et al., 2021)

Symbiosis – Protective Factors:

- **Lactobacillus Species:** Even though they are fewer on the vulva, *Lactobacillus* bacteria still help protect the skin. The most common ones are *Lactobacillus crispatus* and *Lactobacillus iners*. They produce lactic acid, which keeps the skin slightly acidic. This makes it harder for harmful bacteria to grow. They also reduce inflammation, which protects the skin from irritation and damage (Pagan et al., 2021; Javadi et al., 2024). In older women, lower oestrogen levels can reduce these good bacteria even more, which may make things worse (Taylor et al., 2024).

- **Commensal Stability:** The vulva normally hosts many types of bacteria. This is not a problem if they stay in balance. When the good and bad bacteria are in harmony, the skin stays strong and healthy. This balance lowers the risk of long-term irritation and helps prevent the start of serious problems like cancer (Pagan et al., 2021; Pagan et al., 2023).

Healthy skin on the vulva shares some bacteria with nearby areas like the vagina and anus. But in women with lichen sclerosus or high-grade lesions, the bacteria are very different. Some studies also found viruses like *Papillomaviridae* on the skin of these women. This includes cases where HPV was not thought to be the main cause. This shows we still have more to learn about how viruses and bacteria may work together in vulvar diseases (Pagan et al., 2023).

7.6 Mechanisms Linking Dysbiosis to Cancer

Persistent Inflammations: Dysbiosis can lead to chronic inflammation which creates a microenvironment for the development of gynecological cancer (Trifanescu O. G., 2023).

Dysregulation of the Immune System: An imbalance in the microbiota can interfere in the normal immune systems and this disruption can progress to form malignant cells that potentially lead towards cancer (Trifanescu O. G., 2023).

Alterations in the Metabolic: Dysbiosis can lead to metabolic changes which increase the level of estrogen and promote the development of hormone-dependent cancers (Trifanescu O. G., 2023).

Table 2: Dysbiosis and Symbiosis of gynecological cancer

Cancer	Bacteria	Dysbiosis Mechanism	Symbiosis Mechanism	DOI
Cervical Cancer	*Lactobacillus* spp.	Decreased Lactobacillus spp. leads to increased vaginal pH and microbial diversity.	Maintenance of vaginal pH (acidic, <4.5) which inhibits the growth of HPV infection.	https://doi.org/10.3390/diagnostics13050877 https://doi.org/10.1016/j.arcmed.2017.11.008 https://doi.org/10.3389/fcimb.2024.1330844 https://doi.org/10.1093/infdis/jiz325
	Gardnerella spp.	Forms biofilm formation and leads to persistence of HPV infection.	Not reported	https://doi.org/10.3389/fmicb.2021.767931
	Prevotella spp.	Significant increase in *Prevotella* influences the progression of cervical cancer.	Not reported	https://doi.org/10.3390/genes14040936
	Sneathia spp.	In response to HPV infection the richness of Sneathia increased.	Not reported	https://doi.org/10.1186/s13027-024-00590-7
	HR-HPV-(16,18)	DNA impaired and tumor suppression disrupted because of HPV (E6, E7 oncoproteins).	Not reported	https://doi.org/10.1128/jvi.78.21.11451-11460.2004 https://doi.org/10.1002/path.2192 https://doi.org/10.1371/journal.pone.0302270
Endometrial Cancer	*Lactobacillus* spp.	Decreased *Lactobacillus* spp. leads to increased microbial diversity.		https://doi.org/10.1038/s41467-017-00901-0
	Atopobium vaginae	According to one theory, it causes persistent inflammation, which both promotes and	Not reported	https://doi.org/10.3390/jpm11070659 https://doi.org/10.3390/diagnostics13050877

		causes local immunological dysregulation.		
	Porphyromonas spp.	Intracellular infection facilitated by *Porphyromonas* species due to immune dysregulation. Moreover, *Porphyromonas* spp. and high pH in the vagina is a promising biomarker for endometrial cancer.	Not reported	https://doi.org/10.3390/jpm11070659 https://doi.org/10.1016/j.ygyno.2017.03.179
	Bacteroides spp.	Not reported	Present as normal flora of endometrium.	https://doi.org/10.3390/jpm11070659 https://doi.org/10.1002/ijc.33428
Ovarian Cancer	*Lactobacillus* spp.	Not reported	It also regulates immune homeostasis, prevents chronic inflammation and inhibits pathogen growth.	https://doi.org/10.3390/pharmaceutics15030948
	Chlamydia trachomatis	Chronic inflammation of the reproductive tract caused by sexually transmitted bacteria, *Chlamydia* spp., has been linked to ovarian cancer.	Not reported	https://doi.org/10.3390/diagnostics13050877
	Proteobacteria	Relative abundance of *Proteobacteria* increased in patients.	Not reported	https://doi.org/10.1080/19490976.2023.2221093 https://doi.org/10.1038/s41598-018-38031-2
	Actinobacteria spp.	Abundance of *Actinobacteria*, especially	Not reported	https://doi.org/10.1080/19490976.2023.2221093

		Bifidobacterium, decreased.		https://doi.org/10.1038/s41598-018-38031-2 https://doi.org/10.2174/1871530322666220509034847
	HPV	HPV-induced dysbiosis in ovarian cancer involves persistent infection, immune evasion, epithelial disruption, chronic inflammation, and altered viral-microbiome interactions, creating a tumor-promoting environment.	Not reported	https://doi.org/10.18632/oncotarget.16717
Vaginal Cancer	*Lactobacillus* spp.	Increased presence is linked with instability of the microbiome	It decreases the pH of vagina by producing lactic acid, inhibits growth of pathogen and maintains epithelial barrier integrity	https://doi.org/10.3390/genes14040936
	Gardnerella vaginalis	Promotes inflammation	Not reported	https://doi.org/10.3390/genes14040936
	Prevotella timonensis	Weaken mucosal immune defense	Not reported	https://doi.org/10.3390/genes14040936
Vulvar Cancer	*Fusobacterium nucleatum*	Promotes tumour growth and helps vulvar cancer advance faster.	Not reported	https://doi.org/10.1186/s12967-023-04113-7
	Pseudomonas aeruginosa	Cancer proliferation and poor patient survival in vulvar squamous cell carcinoma.	Not reported	https://doi.org/10.1186/s12967-023-04113-7
	Actinomyces spp.	Higher abundance linked to chronic inflammation in	Not reported	https://doi.org/10.3389/fmicb.2023.1264768

		lichen sclerosus, a precursor to vulvar cancer.		
	Ezakiella spp.	Detected in higher levels in lichen sclerosus cases, suggesting role in inflammation-related carcinogenesis.	Not reported	https://doi.org/10.3389/fmicb.2023.1264768

8 Possible Therapeutics Targeting Microbiota

New treatment possibilities for female reproductive cancers have been introduced through the research on microbiomes. Cervicovaginal microbiota, which are essential for preserving vaginal health and wellbeing, is one example. According to research, it affects HPV persistence, a primary cause of cervical cancer, and controls immune responses (Ntuli, 2022) (Kyrgiou M. &., 2022). To restore microbial balance and lower the risk of cancer, microbiota-based therapeutics are now being studied extensively. The therapies involve immune modulation, microbiome-targeted pharmaceuticals, microbiota transplantation, and probiotics. The brief discussion on these therapies is provided below.

8.1 Probiotic Treatment

Probiotic treatment is one of the most studied treatments. The *Lactobacillus* species make up most healthy vaginal microbiomes. These species maintain a beneficial acidic environment in the vagina. *Lactobacillus crispatus* and *Lactobacillus iners* produce lactic acid. Lactic acid reduces the growth of pathogenic bacteria and decreases the persistence of HPV (Alimena, 2022) (Siddiqui, 2022). Research indicates that a simple probiotic supplement may restore the healthy vaginal microbiome in women exhibiting dysbiosis. Thus, the risk of lower HPV-related cancer could be significantly lowered (Bowden S. J., 2023) (Zeber-Lubecka N, 2022). Some research suggests that probiotics may improve the effects of chemotherapy and radiation therapy. Treatment resistance might have been linked to tumor-resident bacteria like *Lactobacillus iners* (Colbert L. E., 2023).

8.2 Vaginal Microbiota Transplantation (VMT)

This is a similar method to Fecal Microbiota Transplantation (FMT) which is used to treat gut dysbiosis. VMT involves the transplantation of a healthy vaginal microbiome from a donor to a patient exhibiting microbiome dysbiosis (Zhou Z, 2024) (Norenhag J, 2020). Research highlights that VMT might help restore a *Lactobacillus* dominant microbiome. Therefore, the presence of harmful bacteria could be significantly reduced which might link to cancer (Curty, 2019) (Kyrgiou M. &., 2022). However, its long-term safety and effectiveness are still a debate and need more research in the field.

8.3 Immune Modulation

It is an emerging approach. The cervicovaginal microbiota affects local immune reactions by affecting cytokine production and immune cell activity (Huang, 2024) (Liu, 2023). Cancer risk is significantly increased when some microbes cause chronic inflammation. Research has been developed to target harmful bacterial communities and reduce inflammation and anti-tumor immunity (Akbari, 2023) (Wang J, 2020). Alternatively, some scientific researchers are developing genetically modified *Lactobacillus* strains. The expectation is the prevention of cancer progression through delivering immune-boosting molecules (Chalif, 2024) (Kakotkin, 2023).

8.4 Microbiome-targeted Drugs

Microbiome-targeted Drugs involves in the process of protecting beneficial bacteria and eliminate harmful bacteria. Common antibiotics assert negative consequences by disturbing the whole microbiome (Akbari, 2023) (Chen Y, 2020). *Bacteriophages* can be an alternative option in this case. This category of viruses aims to destroy pathogenic bacteria and help preserve useful microorganisms (George, 2023) (Zhang, 2021). Therefore, removal of cancer associated bacteria without disturbing the vaginal ecosystem could be achieved through this approach.

8.5 Metabolite-based Therapy

Metabolite based therapy is a promising and emerging therapy. Some beneficial metabolites are proven to be used as therapeutic agents. Short-chain fatty acids, shortly known as SCFA, have shown significant anti-inflammatory and anti-cancer properties. These SCFAs are considered beneficial metabolites. For example, Butyrate is a SCFA, and it can regulate cancer related gene expression and promote cell death in tumors (Pourmollaei, 2020) (Zhou Z, 2024).

It is understood from studies that microbiome-based treatments are still in early development. Microbiome composition varies greatly and varies from person to person. Therefore, developing any standardized therapies is even more challenging (Zeber-Lubecka N, 2022). To verify the long-term effects of these treatments, more clinical trials are required. Regulatory approval is also a challenge, especially for engineered probiotics and microbiota transplantation (Chen Y, 2020) (Kyrgiou M. &., 2022).

Even with these challenges, microbiota-based therapies offer a new direction for cancer prevention and treatment. Combining microbiome therapies with traditional cancer treatments could improve outcomes for patients. These approaches could also reduce the global burden of cervical cancer (Huang, 2024) (Musa, 2023). More research and collaboration across different fields will be necessary to bring these innovations into clinical use.

9 Discussions

The study focuses on the importance of microbiomes in gynecological cancers and the relationships between microbial populations and cancer formation. It applies a cross-disciplinary strategy that embraces microbiology, oncology, and immunology to reveal how microbial dysbiosis contributes to cervical, endometrial, ovarian, and vaginal cancers. According to the study, a rise in harmful bacteria and a decline in Lactobacillus species can lead to chronic inflammation and an increased risk of cancer. Additionally, it examines potential treatments based on the microbiome, including immune regulation, vaginal microbiota transplantation, and probiotics. Nevertheless, there are drawbacks, such as variations in study methodologies, challenges in proving cause and effect, and difficulties integrating microbiome-based treatments into clinical settings. Biomarkers are very important in cancer diagnosis, including HPV DNA for cervical cancer, MSI for endometrial cancer, CA-125 and HE4 for ovarian cancer, and microbial markers are coming up as potential diagnostic markers. New diagnostic technologies including liquid biopsies, artificial intelligence-based imaging, and microbiome sequencing are improving the current techniques for early diagnosis. Programs such as Pap tests, HPV testing, and colposcopy are still important, but the analysis of the microbiota may become a method of cancer diagnosis without contact. Microbial biomarkers and advanced diagnostics can be integrated to transform the practice of gynecological cancer screening and care. To prove the efficacy of microbiome-based therapies and incorporate them into cancer treatment, additional investigation and clinical studies are required.

9.1 Strengths

Comprehensive and multidisciplinary perspective: The research and analysis involve diverse research disciplines and cover a range of academic subjects. Some of these include microbiome science, oncology, immunology, molecular biology etc. However, this inclusion altogether provides a general understanding of cervicovaginal microbiomes in reproductive cancers (Castanheira, 2021) (Kyrgiou M. &., Vaginal microbiome and cervical cancer, 2022) (Curty G, 2019). This approach of study improved the reliability and subject relevance of the study.

Robust evidence on microbiota-cancer interactions: The research put emphasis on the role of Lactobacillus depletion and pathogenic microbial overgrowth in cervical carcinogenesis. This is in fact supported by studies that identified specific microbial signatures in HPV-positive and HPV-negative patients (Liu, 2023) (Huang, 2024) (Chen S. L., 2021). In addition to that, the study discusses the influence of tumor-resident bacteria on chemotherapy resistance, metabolic pathways, and inflammation (Colbert L. E., 2023).

Exploration of microbiomes as a diagnostic and therapeutic tool: The research explores the ability of microbiome diversity and dysbiosis as both are the indicators for early cancer diagnosis. The study also highlights the possible associated treatment targets (Zeber-Lubecka N, 2022) (Zhou Z, 2024). The study investigated several therapeutics which include probiotics, fecal microbiota transplantation, and microbiome-based immunotherapy. These therapeutics analysis and study present promising interventions, demonstrating the translation potential of the conducted study (Siddiqui, 2022) (Akbari, 2023).

Consideration of host microbiome-immune interactions: The research combines observations on how microbiota changes the immune system and in the same time influences HPV persistence, inflammation, and immune evasion mechanisms in cervical cancer (Ntuli, 2022) (Wang J, 2020). These insights gained through detailed in-depth study provide a systematic understanding of how microbial communities interact with host immunity to drive carcinogenesis (Bowden M. V.-d.-B., 2023).

Public health and preventive strategies: Research has shown that important public health initiatives include microbiome-targeted therapies, cervical cancer screening programs, and HPV vaccination (Kakotkin, 2023) (Nguyen, 2024). In cancer prevention and treatment, the

detailed study improves the conversation. This also includes contribution to the discourse on health equity and accessibility (Chalif, 2024) (Musa, 2023).

Clinical and global health relevance: Cervical cancer incidence remains high in the low-middle income countries; thus, the research results are more appropriate for the global oncology procedures (Chambers LM, 2021) (Han X, 2024). The study prioritizes the impact on health policies, preventive care, and future research directions. This also opens the scope of further studies and research related to the field.

9.2 Limitations

Variability in microbiome research methods: The study focuses mainly on the lack of standardization of microbiome research. Microbiome research lacks differences in sampling techniques, sequencing platforms, and bioinformatics approaches that affect study reproducibility (Akbari, 2023) (Chen Y, 2020) (Zeber-Lubecka N, 2022). However, these inconsistencies are operational and pose a challenge for cross-study evaluations.

Challenges in establishing causality: Much of the research related to cervical microbiome and the potential for cancer is descriptive and representative. Thus, it becomes complicated to establish the relationship between these two factors (Huang, 2024) (Zhou Z, 2024). Prolonged and long-term intervention studies are necessary to understand if modifications in microbiota anticipate cancer development.

Confounding factors in microbiome-cancer links: The microbiome is mostly influenced by a wide range of external variables, for example, antibiotic usage, sexual behavior, nutrition, hormones, socio environmental conditions etc. Direct microbial contributions to the risk of cancer can be concealed due to these factors (Curty, 2019) (Kyrgiou M. &., 2022). These confounding variables control the applicability of findings among communities.

Limited integration of microbiome therapies into clinical practice: Microbiota-based therapies have not been significantly integrated into cancer therapy procedures though continuous study has been commenced. These therapies include probiotics, microbiome transplants and engineered bacterial medicines. Their restricted application is connected to concerns over regulation, safety and efficacy (Pourmollaei, 2020) (Zhang, 2021). The transition from experimental studies to clinical applications continues to pose significant challenges.

Healthcare disparities and accessibility issues: This study emphasizes discrepancies in cervical cancer prevention, availability to HPV vaccine and microbiome-based diagnostics. All these discrepancies are nurtured in resource-constrained environments (Kakotkin, 2023) (Nguyen, 2024). These discrepancies inhibit the significant implementation of microbiome-based preventative therapies. Thus, the discrepancies necessitate policy-driven healthcare solutions (Musa, 2023).

10 Conclusions

Microorganisms remain an important concern in causing various gynaecological cancers in females. *Lactobacillus* has been found as an indicator of healthy microbiota of the female reproductive tract whereas, presence of microorganisms like *Gardnerella spp., Prevotella spp., Sneathia spp.,* HR-HPV-(16,18) contributes to dysbiosis of the cervix causing cervical cancer. Dysbiosis in the endometrium is caused by *Atopobium vaginae, Porphyromonas spp., Bacteroides spp.* leading to endometrial cancer. *Chlamydia trachomatis, Proteobacteria, Actinobacteria spp.,* HPV is proved to cause dysbiosis in the ovary leading to ovarian cancer. The dysbiosis in the vagina leading to vaginal cancer is caused by *Gardnerella vaginalis, Prevotella timonensis. Fusobacterium nucleatum, Pseudomonas aeruginosa, Actinomyces spp., Ezakiella spp.* are known to cause vulvar cancer as they are responsible for dysbiosis in the vulva. Studies on gynaecological cancers shows the greater presence of Gram-negative bacteria like *Porphyromonas spp., Bacteroides spp., Fusobacterium nucleatum, Pseudomonas aeruginosa* and many more in causing gynaecological cancers over Gram positive bacteria like *Actinomyces spp., Ezakiella spp.*

With the use of modern diagnostic techniques, the mortality risk in females from malignancies of the female reproductive system can be decreased. This could be done by Pap test, HPV screening, CTNG testing, gene sequencing, biopsies, MRI or CT scans and many more. Not only can the presence of biomarkers in patients' samples lead to diagnosing gynaecological cancers. In addition to numerous diagnostic techniques, effective therapeutic and preventive vaccines may be developed alongside awareness campaigns to drastically reduce and control all types of female reproductive cancers.

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