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Review

Association between the microbiota and women's cancers – Cause or consequences?

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ABSTRACT

Breast, ovarian and uterine cancers are the most common neoplasms among women. Several mechanisms may be involved in oncogenesis and these include environmental and genetic factors. Bacteria may affect the development of some cancers, with bacterial components, their products and metabolites interacting with susceptible tissues. Commensalism and dysbiosis are important potential mechanisms involved in oncogenesis, and an effective strategy for diagnosis and treatment is required. The purpose of this review was to analyze the complex associations between these cancers in women, and the microbiota, specifically bacterial microbes. However, several cancers have an increased prevalence among individuals with HIV and HPV so the relationship between viral infections and malignancies in women is also referred to. We described how different phylum of bacteria, particularly in the gut, mammary tissue and vaginal microbiome may be involved in carcinogenesis; and we discuss the potential pathways involved: (I), that lead to cell proliferation, (II), immune system perturbation, (III), cell metabolic changes (e.g., hormonal factors), and (IV), DNA damage. Studies investigating the differences between the composition of the bacterial microbiota of healthy women compared to that present in various conditions, and the clinical trials are summarized for the few studies that have addressed the microbiota and related conditions, are also reviewed.

1. Introduction

Originally, the term microbiota was intended to describe an ecological community of symbionts, commensals, and pathogenic microbes living within the human body. [1]. The totality of microbiota including bacteria, fungi, archaea, protists, and viruses colonize the human body at birth [2,3] where they establish a mutually beneficial host-microbiome relationship [1]. This can be seen in specific sites of the human body including the vagina, gut, skin, and urethra [4]. Gender may be one of the most important variables that affects microbiota. It has been reported that there are differences between the number of bacterial cells ratio with that of human cells in men and women (about 1.3:1 in men (38×10^{12} and 30×10^{12}, respectively) and about 2.2:1 in women (44×10^{12} and 21×10^{12}, respectively) [5]. Sex hormones have been reported to affect the gut microbiota in adolescence and this impact is sustained into adulthood. Specific probiotic bacteria are have been used in the treatments of some cancers in animal models, and it has been reported that they can reduce tumor proliferation and modulate inflammation (Fig. 1, A) [6]. However, malignancies are caused by multiple interactions including hormonal and immune factors;

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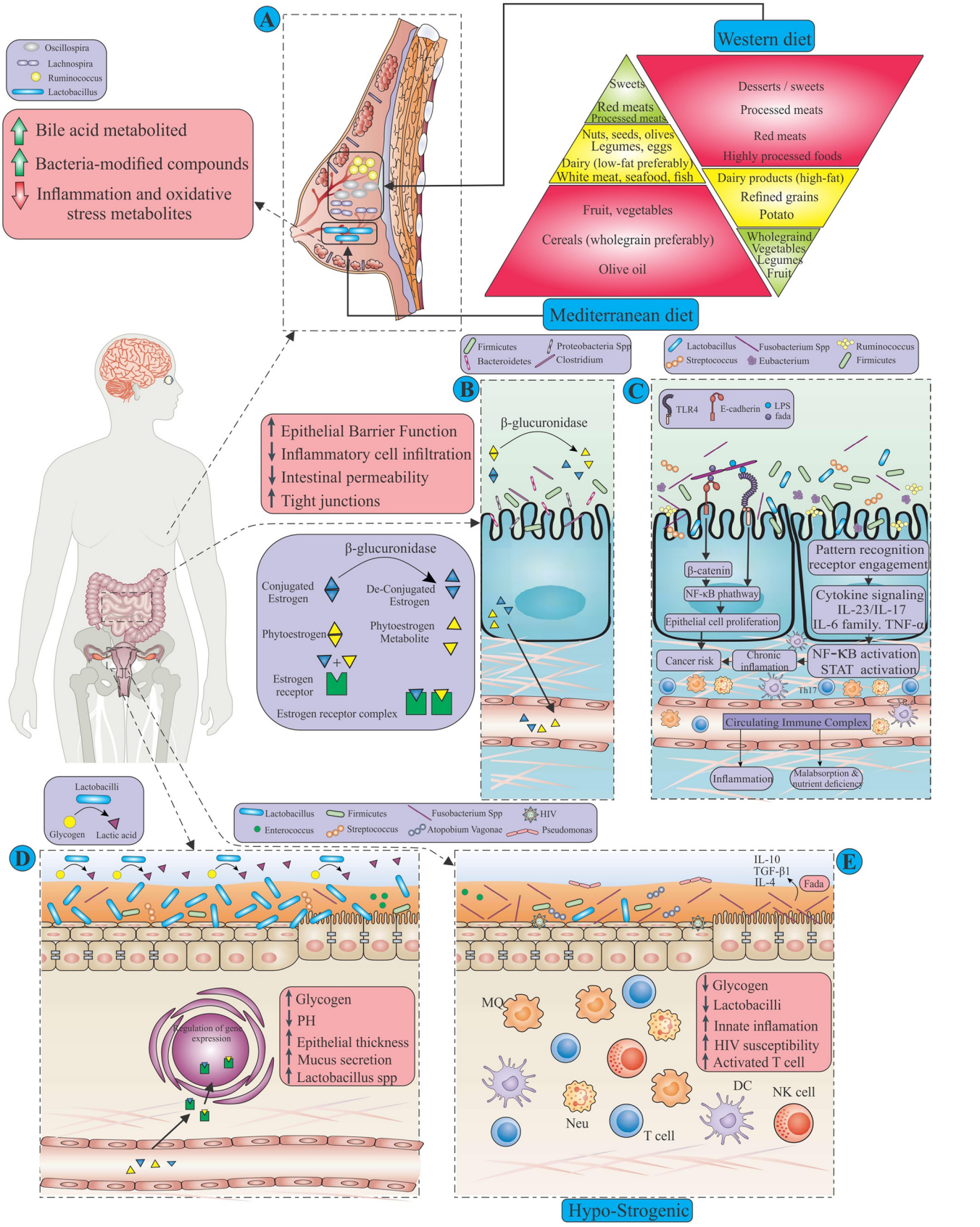

Fig. 1. Possible interactions between bacteria and tissues. Diet has a significant effect on the mammary bacteria. Despite the pathogenic effect, the figure also shows different bacterial profiles in breast tissue that some may be beneficial via their indirect role in breast cancer prevention through the reduction of inflammation and oxidative stress metabolites (A). The gut microbiota regulates estrogens through secretion of β-glucuronidase. β-glucuronidase de-conjugates estrogen to enable the binding to estrogen receptors (B). Microbes through might promote cancer by triggering uncontrolled innate and adaptive immune systems via specific epithelial receptors and penetrate into submucosa layer that can mediate inflammation responses through mediators including cytokines and chemokines (C). Pathways by which the microbiome could prevent or develop infections as well as carcinogenesis via immune deregulation has shown (D, E).

furthermore, several groups of cancers are caused by disruption of the microbial community, which is termed dysbiosis [7,8]. Cancer is one of the most serious public health issues worldwide. The statistics of new cancer cases and mortalities in the United States in 2019 caused by female hormone-sensitive cancers (provided by The National Center for Health Statistics) has estimated that breast carcinoma is one of the most common cancers followed by uterine and ovarian cancers [9]. There is a complex association between cancers and microbes. Despite the fact that cancers are mainly attributable to genetics and environmental factors (e.g., diet, alcohol, smoking and radiation), it has been estimated that approximately 2 million new cancer cases were caused by infections [10,11]. Generally, carcinogenesis can be influenced by bacteria via four pathways: (I), by stimulating cell proliferation and/or death, (ii), perturbation immune system function, (iii), impact on the metabolism within a host cell [11], (iv), genomic stability and DNA damage [12]. Thus, bacteria can influence the development of cancers by interacting with the tissue using bacterial components, products and their metabolism (e.g., estrogens) [13]. The role of the microbiome in cancer development, as well as estrogen-mediated cancers, will be considered in this review.

2. Search methods for review

The databases below were searched from the beginning up to March 2020: Embase and MEDLINE through OvidSP, Science Core Collection website, Scopus database and Google Scholar. To find grey literature, OpenGrey website was used. Algorithm for electronic search included terms that refer to the some of the important keywords “Female cancer”, “Female malignancy” “microbiome” “microbiota” “microbial communities” “breast dysbiosis” “vaginal dysbiosis” and “uterus dysbiosis” et cetera. A manual search was used to find reference lists of related articles and reviews. This manual search was performed to identify articles not found by the electronic search. In cases where it was necessary, the authors were contacted to obtain more information. There was no language restriction for searching or selecting the articles.

3. Functional pathway

3.1. Host cell proliferation and death

Cyclomodulins are a group of bacterial toxins. Cell-cycle progression can be deregulated by the action of these toxins in the host which are divided into two groups: stimulatory cyclomodulins (that are cell proliferation promoters) and inhibitors with their cell-cycle blocking function [14]. Additionally, human oncoviruses are pathogens that can trigger a transformation in the cells of the host. They can also lead to carcinogenesis through the insertion of oncogenes into the genomes; for example, human papillomaviruses express oncoproteins E6 and E7 [15]. CD97, encoded by the Adhesion G Protein-Coupled Receptor E5 (ADGRE5), is the most commonly expressed member with functions in cell adhesion, migration, and regulation of intercellular junctions. CD97 is also found in a variety of human cancers, including thyroid, brain, and gastric cancer [16]. Cell proliferation may be promoted via an exosome-mediated MAPK-signaling pathway [16]. Also, exosomal miRNAs are involved in the activation of the CD97-associated pathway [17,18]. CD97 up regulation is positively correlated with tumor metastasis in hepatocellular carcinoma which may be the result of intestinal bacteria [19]. The gut microbiota and toll-like receptors are able to promote the hepatocellular carcinoma by mediating increased proliferation. Functionally, CD97 may also promote cell migration [19,20].

3.2. Immune system

Microbes might promote malignancy by triggering an unregulated innate and adaptive immune system response [21]. Inflammatory mediators including cytokines and chemokines have direct effects on a tumor, and contribute to several hall-marks of cancer [22]. Cancer-associated microbes may target the Wnt/β-catenin signaling pathway. In regards to colon cancer, for example, bacteria adhere to the epithelial cell through FadA adhesion to invade and induce inflammatory response and oncogenic, which stimulate the growth of cells. FadA triggers β-catenin activation by binding to E-cadherin of the host cell, so the inflammatory and oncogenic responses will regulate differently. In an evolving tumor, pro-inflammatory pathways are involved in the breach of the mucosal barrier. When the boundaries between the host cell and microbe collapse, receptor recognition patterns and the signaling cascades may engage. NF-κB and STAT3 signaling regulate the feed-forward loops of chronic inflammation that are associated with cancers (Fig. 1, C) [11,23]. There is another mechanism by which the susceptibility to HIV is enhanced via the breaking down of the epithelial barrier of the vagina followed by the action of vaginal bacteria. These bacteria promote pro-inflammatory cytokines secretion during the epithelial cell response to HIV, which may result in decreased trans-epithelial resistance (Fig. 1, E) [24].

With regards to the gastrointestinal tract, tight epithelial cell junctions reduce gut inflammation. The tight junctions prevent the entry of microorganisms and their effect in inflammatory bowel disease (IBD). Accordingly, Urolithin-A (an anti-inflammatory factor) can provide protection against colitis by repairing the damaged gut barriers that may be useful in the treatment of inflammatory disease. One report has shown that Urolithin-A can be generated from a compound extracted from pomegranates, known as ellagic acid (EA), by the strain *Bifidobacterium pseudocatenulatum* INIA P815 in the gastrointestinal tract [25].

Carrega et al. [26] have examined the association between microbiota and regulation of immunity in cancer. The *lactococcus spp*. can maintain the cytotoxic activity of natural killers (NK) to modulate cellular immunity [26]. Other studies have shown that the host immune response is the main cofactor in inducing different diseases such as Helicobacter-related disease. Accordingly, several members of the toll-like receptors (TLR2 and/or TLR) are involved in the recognition of Helicobacter in the innate immune system [27]. Moreover, HIV-I risk can be modified by vaginal bacteria that can alter local inflammation. The secretion of pro-inflammatory cytokines, such as TNFα, IL-8, IL-1α, IL-1β, and RANTES is induced by several bacteria including *Aerococcus, Fusobacterium*, *Gemella, Sneathia*, *Prevotella,* and *Mobiluncus* by the activation of Toll-like receptors. These cytokines appear not be induced while the epithelial cells of the vagina are cultured with *L. crispatus* that is protective against HIV, or other commensals of the vagina [24]. There have been few studies that have studied women with gynecological malignancies. One study found that during the study period, fifty-seven women with HIV were diagnosed with concomittent gynecologic cancers: 46 % with cervical cancers, 16 % with ovarian cancers, 12 % with endometrial cancers, and the rest 26 % with other gynecologic cancer. 52 % women of these were diagnosed with stage I disease, and 47 % with stage II–IV disease (Table 1) (28).

3.3. Metabolic function

In breast cancer, the gut microbiota may influence its pathogenesis through effects on endogenous estrogens. The parent estrogens and their metabolites are conjugated and excreted into urine or bile; they ultimately pass into the distal gut, in which some are deconjugated and

Table 1
Characteristics of HIV infected Gynecologic Cancer Patients.

	Cervical (45 %)	Ovary (15 %)	Uterine (12 %)	Total
Stage I	(61 %)	(11 %)	(71 %)	(52 %)
Stage II–IV		(89 %)	(28 %)	(47 %)

influenced by resident microbe through several plausible mechanisms. Therefore, the association appeared to be stronger for estrogen metabolites than for the parent estrogens. Most of these taxa have been identified as belonging to the *Firmicutes* or *Bacteroidetes* phylum [29].

3.4. DNA damage

Microbes also trigger transformation by disrupting the stability of genome, cell death resistance, and proliferative signals. To survive in thir environment, several mechanisms have been used by bacteria to damage the host DNA; such defensive bacterial factors can contribute to carcinogenic mutational events [11]. Moreover, some bacterial species may contribute to chronic inflammatory disease by increasing reactive oxygen species production that may eventually mediate genotoxicity. Carcinogenesis can also be modulated by releasing different bacterial toxins that cause DNA damage. As bacteria cross the epithelial barrier, they can directly insert the toxins into the cell of the host. Various bacterial toxins such as *Bacillus fragilis*, *colibactin*, and *cytolethal* cause a carcinogenic cell responses; specifically against DNA damage [30].

4. Breast cancer

Breast cancer (BC) is the most prevalent cancer among females [31]. The annual rate of female breast cancer mortality is estimated at approximately 41,760 cases per annum in the United States of America [9]. Breast cancer has many risk factors. Fewer than 10 % of breast cancers are attributed to genetic mutations [32]; BRCA1/2 gene mutations are one cause for example [33]. Also, it may also be associated with environmental, hormonal, and lifestyle factors [32,34]. There is a common form that shows the essential role of endogenous estrogen in breast cancer development [35]. It can have an effect through a high level of estrogen and its metabolic differences [36]. As the estrogen receptor-beta (ER-beta) has been detected in the oral mucosa and salivary glands, levels of female sexual hormones influence the composition of the microbiota in gut and also oral cavity may cause breast cancer [37]. Furthermore, it has been shown that some bacterial groups may be additional environmental factors that are involved in the development of a tumor through deregulation of signals/pathways in estrogens circulation [38,39]. In general, circulating estrogens are bioactive. Estradiol and estrone are the main circulating estrogens. The main estrogen produced during pregnancy is estriol while the most biologically active estrogen is estradiol in the human body, and is secreted by ovarian granulosa cells. Estradiol, estrone, and estriol are produced in peripheral tissues through aromatization and dehydrogenases. During the hepatic phase II metabolism, estrogens are conjugated by glucuronic acid and sulfate enzymes such as UDP-glucuronosyltransferases and sulfotransferases. After the conjugation, these hormones may be excreted in the feces or urine after becoming water-soluble or may turn into a lipophilic moiety. Conjugated estrogens are excreted into the bile. They can also be found in intestines [13,35]. So, The gut microbiota is able to regulate estrogens through secretion of β-glucuronidase [40]. Recent advances have indicated that the interaction of estrogens and gut microbiota may be associated with obesity, diabetes, and cancer [41]. Moreover, it has been suggested that the microbiota of breast cancer patients is different compared to that of healthy females, demonstrating that certain bacterial communities are associated with the development of cancer as they are recognized in carcinogenic tissue [42].

5. Gut microbiome

The human intestine contains approximately 100 trillion gut microbiota, comprising approximately 500–1000 different species [43]. Gut bacteria have long been considered essential in human health, such as supplying nutrients, producing vitamin K and vitamin B, digesting and absorbing indigestible carbohydrates (fibers), and promoting angiogenesis and enteric nerve function. However, they can potentially be harmful [44]. Gut microbiota composition in the over 70 s may be affected by changes in the physiological function of the gut [5]. However, their symbiotic relationship, termed “normobiosis”, with the host maintain a balance within the gut. A disruption in the balance, known as “dysbiosis”, under abnormal conditions is assumed to have deleterious consequences for the host [45]. For instance, several studies analyzing the association between the gastrointestinal microbiome and breast cancer [42]. The implication is that breast cancer is associated with estrogen-dependent functions of the gastrointestinal microbiome [46]. Many studies are investigating the relationship between breast cancer and gut microbiome. In 2011, researchers discussed the so-called “estrobolome” which is known as the gut microbiota gene repertoire, whose products metabolize estrogen and its metabolites [47]. Estrogens are deconjugated by gut microbiota via bacterial secretion of β-glucuronidase to enable the binding to estrogen receptors (Fig. 1, B) [47]; then, they are reabsorbed as free estrogens and reach tissues like the breast [42]. The effect of the microbiota is influenced by several factors such as genetic, epigenetic, and environmental factors such as diet (Fig. 1, A) [45]. For instance, it has been shown that dietary fiber may be effective in the composition of gut bacteria and reduce the activity of intestinal β-glucuronidase, so that the re-absorption of estrogen followed by deconjugation process may be reduced [48]. It is worth mentioning that, according to recent studies in mouse models, inhibiting microbial β-glucuronidase does not prevent the breast carcinogenesis [49]. Estrogen receptor-positive breast cancer is the most common subtype of breast cancer [50]. Most effects are mediated via two estrogen receptors: estrogen receptor alpha (ER-alpha) and beta (ER-beta). ER is the protein that is expressed in 50–80 % of mammary tumors, while ER is more abundant in normal human mammary glands. Breast cancer is classified based on gene expression profiles into four types: (I), overexpression of human epidermal growth factor receptor 2 (HER2), (ii), Triple-negative carcinoma (TNC) which are negative for HER2, ER and PR, (iii), Luminal A (ER and PR positive, low proliferation rate), (iv), Luminal B (ER and PR positive, high proliferation rate) [51]. The number of cells entering G0 and G1 increases as a result of estrogen receptor activation and this stimulates proliferation, which can be identified in breast cancer [52]. A diverse community of microorganisms colonizes the human gastrointestinal tract [53], so it can be considered as the best choice to investigate the microbiota and a model to investigate the interactions between host and microbiota, which may cause disease. The main genera of gut microbiota are: Lactobacillus, *Bacteroides*, *Faecalibacterium*, *Clostridium*, *Eubacterium*, *Ruminococcus*, *Peptococcus*, *Peptostreptococcus*, *Streptococcus*, *Streptomyces* and *Bifidobacterium*. In addition, various studies have suggested an interaction between gut microbiota and estrogen. Bilateral ovariectomy in humans has been reported to be associated with the higher abundance of *Clostridium bolteae* [5]. In men as well as postmenopausal women (but not in pre-menopausal women), there was a significant relationship between total urinary estrogen level and richness and α-diversity of intestinal microbiota [5]. Higher levels of non-ovarian systemic estrogens was related to the greater fecal *Clostridia* (consisting of *non-Clostridiales* and three genera in the family of *Ruminococcaceae*). Furthermore, by sequencing the 16S rRNA, more than 90 % of bacterial species within the gut were found to be *Bacteroidetes* and *Firmicutes*, as well as *Proteobacteria* [38,53]. Specifically, many β-glucuronidase bacteria can be found in two sub-groups that belong to the Firmicutes phylum, the *Clostridium coccoides* group, and the *Clostridium leptum* group. Also, a member of *proteobacteria* phylum, the *Escherichia/shigella* bacterial group, can possess β-glucuronidase enzymes [54]. Moreover, according to experiments on feces from 32 breast cancer patients, Bard and colleagues [55], estimated the absolute numbers of *Bifidobacterium* and *Blautia*, and found that *F.Prausnitzii* (*faecalibacterium* genus) and *Blautia* were differed in proportion, dependent on the clinical stages of disease. It has been indicated from staging study that in comparison with grade I breast cancer patients, women with grade III cancer were

detected with a higher absolute count of Blautia [55]. In addition, Goedert et al. [56] studied 19 feceal samples and urine from 48 post-menopausal women with breast cancer and 48 controlled women. It was found that the gut microbiota detected from patients with breast cancer was higher in the level of *Clostridiaceae*, *Faecalibacterium* and *Ruminococcaceae* (beta diversity) while the levels of *Dorea* and *Lachnospiraceae* (alpha diversity ($P \leq 0.004$)) which was estrogen- independent were lower compared to controlled women. Also, a higher level of systematic estrogen was found in patients. In controls, total urinary estrogen was correlated with the alpha diversity but not in cases [56]. Fuhrman et al. [29] studied 60 healthy postmenopausal women and claimed that women with a more diverse gastrointestinal microbiome, particularly four *Clostridia* taxa, have shown to have a high proportion of hydroxylated estrogen metabolites to parent estrogens in the urine. These diff ;erences in results of breast cancer and the diversity of gastrointestinal microbiota can prove the effect of the disease stage on the microbiota [37].

Goedert et al., have reported that the association between the gut microbiota and breast cancer is related to inflammation that may lead to IgA production by plasma cells resident in the gut mucosa. By dividing cases into those with IgA + and IgA- microbiota, cancer cases were found to have an altered composition of IgA+, lower richness and alpha diversity of microbiota in feces. Moreover, estrone, estradiol and main estrogen metabolites had a lower level in controls via cases. In comparison with controls, postmenopausal females with BC had a different estrogen-independent relationship with IgA ± microbiota, concluding that the gut microbiota affects BC risk through altering the metabolism, estrogen recycling, and immune pressure [57].

A potential causal role of gut microbiota in the development of obesity using germ-free animals and microbiota transplant has been reported [58] and it is known that obesity is associated with a 35%–40% increased risk of BC recurrence and mortality [59]. It has been reported that BMI is association with the composition of the gut microbiota including the *Firmicutes* and *Bacteroidetes* phyla which were the most numerous, representing 39.4 % and 13.0 % of total bacteria, respectively. The Firmicutes phylum combines the subdominant *C. leptum cluster, C. coccoides cluster, F. prausnitzii* and *R. intestinalis* [60]. However, some gut bacteria may reach the mammary glands via an entero-mammary pathway which involves the translocation of immune cell-mediated bacteria from the mother's gastrointestinal tract into the mammary gland [61,62]. It is noteworthy that soy isoflavones, that have estrogen-like metabolites can structurally alter the composition of the gut microbial community in postmenopausal women. They do this by increasing the concentration of *bifidobacterium* and simultaneously suppressing the non-classified *Clostridiaceae* [63]. It is possible to modulate the gut microbiota by estrogen. However, gut microbiota can also affect estrogen levels. This is via deconjugation of the conjugated estrogens excreted in the bile and its reabsorption by enterohepatic circulation [64]. There is a relationship between increasing serum 25 (OH) D, the the beneficial effects of bacteria and reduced levels of pathogenic bacteria. After vitamin D supplementation, an increase din bacteria associated with a decrease in the activity of inflammatory bowel disease which was dependent on its dose [65]. The environmental bacteria colonization of the gut is associated with immunosuppression induced by HIV [66]. Other Studies have shown that bacterial vaginosis occurs after a shift in *Lactobacillus* dominance to non–Lactobacillus-dominant microbiome contains a high population of *Gardnerella vaginalis* and anaerobic bacteria, such as *Prevotella ssp.*, *Mobiluncus ssp.*,and/or several *Clostridia* species which is related with susceptibility to viral infections and increased HIV infection risk in women and results in poor reproductive health [67]. Other studies demonstrate that there is also a relationship between CD4 + T cell recovery in patients with HIV and gastrointestinal bacterial metabolism through induction in the alterations of the gut microbiome [68]. However, it has been reported that HIV is not capable of targeting bacteria. But, it is worth mentioning that antiretroviral drugs which are used in the HIV infection treatment may affect the gut microbiota. Antiretroviral drugs decrease the abundance of the pathogenic species of the gut that may involve in the modification of lipid and glycan, in order to preserve the colonic cell functions and to be assistance in the integrity of the cell surface [68]. *Gardnerella vaginalis* and other anaerobic bacteria have been evaluated as intervention factors to modify Tenofovir (Antiretroviral drug) gel microbicide effectiveness by biological mechanisms that contribute to increased vaginal inflammation and adherence [67]. Women with HIV are more vulnerable to gynecological and non-gynecological cancers, and cervical cancer is the most common cancer in these patients, and they develop invasive cervical cancer five times more frequently than women without HIV [69]. Also, other research has explained that combined antiretroviral therapy decreased Classical AIDS-defining malignancies and shifted to other non-AIDS-defining malignancies such as anal, lung, colorectal, and liver cancers [70].

6. Mammary microbiome

Some researchers have studied the role of the microbes inhabiting particular human body sites. Xuan et al. [71] observed different levels of *Methylobacterium* and *Sphingomonas* in the tissue of paired normal or/ and healthy women and women with estrogen receptor (ER)-positive breast cancer, suggesting their potential relationship in the development of cancer. In tumor tissue, *Methylobacterium* was enriched, while the absolute levels of bacterium *Sphingomonas* were higher compared to paired normal tissue. However by using qPCR, in all samples, the levels of *Methylobacterium* between tumor tissue and paired normal ($p = 0.2508$) were not different. It has been reported that, in tumor tissue, a higher relative abundance may reflect a decrease in the presence of other bacteria but the absolute level of the organism does not increase. In paired normal tissues, a strong correlation between the abundance of *Sphingomonas* and *Methylobacterium* ($p = 0.0003$) has been reported, which could not be found in the corresponding tumor tissue. It was also suggested that, according to paired normal tissue, *Sphingomonas* and *Methylobacterium* are able to provide a counterbalance in abundance between each other. Meanwhile, the level of *Sphingomonas* becomes lower significantly, while the level of *Methylobacterium* remains steady, in tumor tissue [71]. In contrast, Wang et al. [72] reported that the abundance of *Methylobacterium* was reduced in woman with breast cancer while at the site of the tumor it was reported to be increased in the research done by Xuan et al. [71]. On the other hand, using 16S rRNA sequencing and culture, Urbaniak and colleagues [73] investigated the mammary tissue microbiome. They analyzed breast tissue from 81 individuals of two groups of cases and control women (Canadian and Irish) and collected bacteria from all sites of the breast in women aged 18–90. The main phylum was *Proteobacteria* and in general, *Gammaproteobacteria* (5.0 %), *Prevotella* (5.0 %), *Comamonadaceae* (5.7 %), *Propionibacterium* (5.8 %), *Pseudomonas* (6.5 %), *Staphylococcus* (6.5 %), *Enterobacteriaceae* (8.3 %), *Acinetobacter* (10.0 %), *Bacillus* (11.4 %), and *Enterobacteriaceae* (30.8 %), and were in the most abundant taxa in the Canadian samples. Moreover, in Irish tissue samples, *Pseudomonas* (5.3 %), *Propionibacterium* (10.1 %), *Listeria welshimeri* (12.1 %), and Staphylococcus (12.7 %) were mostly detected. However, they detected Escherichia coli with a high level as an active cancer promoter in BC patients compared with controls. Urbaniak et al. showed that the profiles of bacteria vary in the breast tissue of healthy women, compared to those with BC [73,74]. This idea was similarly suggested by Heiken [75]. Accordingly, malignancy appears to be related to taxa enrichment of normally present in low abundance, including the genera *Atopobium*, *Fusobacterium, Gluconacetobacter, Lactobacillus* (Fig. 1, A), and *Hydrogenophaga*. This research confirmed the distinct existence of breast microbiome and their differences in the breast tissue in malignancies and benign disease. Also, the abundance of Micrococcus, Lactococcus, Prevotella, Corynebacterium, and Streptococcus in healthy women, and Bacteroidetes, Staphylococcus,

Bacillus, Comamondaceae, and Enterobacteriaceae in woman with Breast cancer which caused DNA damage in vitro [75].

7. Ovarian cancer

Many factors including diet [76], inflammation, family history, age, and reproductive factors are involved in determining the risk of ovarian cancer. Cervicovaginal microbiome imbalance has been identified in women suffering from ovarian cancer [77]. Dysbiosis of the microbiome is suggested to be related to pathology issues such as cancers. Ovarian cancer is one of the most lethal malignancies of the reproductive system of women; it affects 1 in 70 women and has the highest mortality rate of the gynecologic cancers. A unique microbiome signature has been identified that is related to ovarian cancer. The results of the pan-pathogen array showed a high significance of a distinct group of viruses, bacteria, fungi and also parasites in ovarian cancer. They detected specific Bacterial Firmicutes signatures in the cancer samples including *Abiotrophia, Bacillus, Enterococcus, Erysipelothrix, Geobacillus, Lactobacillus, Lactococcus, Listeria, Pediococcus, Peptoniphilus and Staphylococcu* [78]. Moreover, Nuno et al. [77] calculated the proportion of lactobacilli species such as *Lactobacillus iners, Lactobacillus crispatus, Lactobacillus jensenii,* and *Lactobacillus gasseri* for each sample, which are essential for the protective low vaginal pH generation, in the cervicovaginal microbiota (Fig. 1, D).

It has found that the occurrence of ovarian cancer, and risk factors of this disease (i.e., BRCA1 germline mutations), were linked with the O cervicovaginal microbiota community [77]. In addition, studies have reported several cases of abdominal pathology in which an elevated serum CA 125 tumor marker may have contributed to the diagnosis of ovarian carcinoma . Nevertheless, tuberculosis was diagnosed after taking peritoneal biopsies and specific tuberculostatic treatment could normalize serum levels of CA 125 [79]. There is another study that suggests that the presence of Chlamydia trachomatis infection in patients with epithelial ovarian carcinomas. Multiple mechanisms can explain the relationship between Chlamydia and cancer development: (I) production of reactive oxygen species which may trigger DNA damage and increase the risk of oncogenesis may increase; (ii) inhibit apoptosis by blocking the release of mitochondrial caspase 3 and cytochrome C, which enables infected cells to escape from the attack of CD8 + killer T-cell and therefore they are less likely to face a normal cell-death process; (iii) Disruption of the normal cadherin – catenin junction structure, which leads to increased exposure to other infections [80].

The associations between the secretory leukocyte protease inhibitor (SLPI), Human epididymis protein 4 (HE4) and a second vaginal protease inhibitor, with the types of vaginal communities of bacteria and with vaginal concentrations of innate immune mediators or proteases have been evaluated. Accordingly, when *Gardnerella vaginalis* dominates a vaginal community, the levels of median vaginal HE4, concentrations of MMP-8, IL-1, IL-1ra, and Mannose-binding lectin (MBL), were the highest. The associations between increased levels of proteases, immune mediators, HE4, and high proportions of G vaginalis suggested that in the female genital tract, bacteria play an indirect role in pro-inflammatory immune response [81]. Evidence shows that a chronic disease development may result in inflammatory profiles of cytokines and chemokines that remain at specific sites. Recent studies report a possible link between bacterial infection and carcinogenesis. It has been hypothesized that Toll-like receptors (TLR) may mediate potential signaling pathways leading to inflammation in cancers. Bacterial products, such as lipopolysaccharide, directly promote the production of pro-inflammatory cytokines and the upgrade of tumor endurance from the ovarian cancer cells [82].

Another hypothesis has proposed an association between the microbial effect on Polycystic Ovarian Syndrome development (PCOS). Gut microbiota dysbiosis may be caused by poor diet that increases the permeability of the gut mucosa, resulting in a rise in the movement of lipopolysaccharide (LPS) from Gram-negative colonic bacteria into the systemic circulation. The subsequent immune system activation interferes with the function of the insulin receptor, enhancing serum levels of insulin that in turn increases the production of androgen action in the ovaries and interferes with the expected development of follicles. Accordingly, the Dysbiosis of the Gut Microbiota theory of PCOS may be responsible for the development of multiple small ovarian cysts [83]. As it also introduced among rodents, the gut microbiota composition was varied from that in the controls. While *Clostridium, Ruminococcus,* and *Lactobacillus* were lower compared to control rats, *Prevotella* was higher among PCOS rats [84].

8. Uterine cancer

Uterine cancer is increasing in incidence and attributable mortality [85]. This cancer can develop via several pathways, including via an inflammatory response, changes in microbiota, or endocrine disruption [86]. In particular, changes in intestinal and vaginal microbiomes can be related with a number of gynecological cancers, including uterine cancer [87]. Based on the research of Tissier [88], it was concluded that a healthy uterine cavity is sterile. Multiple reports have questioned this assumption and it has been shown that the cervical mucus plug is not completely impermeable to vaginal bacterial ascension [89]. The vaginal microbiome consists of a variety of bacterial species between 20 and 140 in particular individuals [90]. Uterine colonization with vaginal bacteria was hypothesized to promote carcinogenesis via microbiota-mediated pathophysiological change in the microenvironment [89]. In fact, the microbiome is considered to participate in oncogenesis by stimulating pro-inflammatory cytokines which are secreted from the host cells or by mediating dysbiosis-related growth factors [21]. Walther-António et al. [91] studied the microbiome in samples which were taken from various sites along the female reproductive tract in women with endometrial hyperplasia and endometrial cancer and patients who were afflicted with benign uterine conditions. Accordingly, microbiome sequencing (16S rDNA) showed that microbiomes of organs, such as the ovaries, cervix, vagina, and Fallopian tubes, are correlated, and there is a systemic microbiome change in cases of cancer and hyperplasia, which can be differentiated from benign cases. In samples that belonged to endometrial cancer, some taxa have detected to be substantially enriched including *Atopobium vaginae* and a *Porphyromonas sp*. which are related to disease development, especially in the presence of a raised level of vaginal pH (> 4.5). Therefore, an increase in vaginal pH was associated with endometrial cancer [91]. It is worth mentioning that, *Lactobacilli* acidify the vagina with lactic acid and may play a role in the reduced incidence of vaginal bacteria and some reproductive tract infections (Fig. 1D) [92]. In addition, several types of lactobacilli may be protective against HIV and the virus is unlikely to develop women with Lactobacillus-dominant vaginal microbiome [24]. Another study has claimed that increased vaginal pH is associated with endometriosis and gonadotropin-releasing hormone (GnRH) therapy suggesting a relationship between the microenvironments of vagina on proliferative uterine conditions that are hormone-driven [93]. For instance, endometriosis is a diseases process that causes inflammation. Features of the disease include endometrial lesions growing outside the uterus that usually affects reproductive age women. It mainly causes dysmenorrhea and infertility but also causes non-cyclical or chronic pain of pelvic as well as dyschezia and deep dyspareunia. Evidence suggests that there is a two-way interaction between endometriosis and the microbiome that is a complex interaction. It seems that endometriosis is related to the increase of *Enterobacteriaceae*, proteobacteria, *Streptococcus* spp. and *Escherichia coli* in different areas of microbiome. It also seems that there is an unclear relation between phylum Firmicutes and the genus *Gardnerella* [94]. Endometriosis is the pathophysiology condition in which estrogen-dependent disease [95]. The “strobolum” is inside the gut microbiome that encloses enteric microbial genes. Products obtained in this process can metabolize

estrogens in gut [96]. Enteric bacteria secretes β-glucuronidase and β-glucosidases that increases estrogen deconjugation [39,96]. This process itself increases free estrogen's reabsorption that lead to higher levels of circulation. In a microbial genome analysis it was determined that there are several microbiome-encoded β-glucuronidase in gut microbiome such as *Bifidobacterium, Bacteroi*des, *Escherichia* and *Lactobacillus* [39]. In particular, it was reported that the genus Escherichia levels were significantly higher in the stools of patients with endometriosis [97]. *Recently, it is not clear that what role the* estrobolome and β-glucuronidase-producing bacteria play in endometriosis. But it is said that a dysbiotic gut microbiome that increases estrogens deconjugation followed by increased levels can create an environment with hyper estrogenic activity that in turn causes the development of endometriosis [94]. The level of *Gardnerella*, *Streptococcus*, *Escherichia*, *Shigella* and *Ureoplasma* (all comprise potentially pathogenic species) *are* increased in the cervical microbiota with stage III–IV endometriosis [97]. There was a greater dominance of *Escherichia/Shigella* in stool samples of women in the group of stage III–IV endometriosis [97]. The relative abundance of gastrointestinal (GI) microbiota can vary over the lifetime of the host and it is worth to say that, the maternal bacteria that are obtained during vaginal delivery can influence the disease. Generally, the gastrointestinal (GI) microbiome has five main bacterial phyla: *Actinobacteria, Bacteroidetes, Firmicutes, Fusobacteria,* and *Proteobacteria*. Such bacteria comprise about 90 % of the total microbiota in the intestine [98]. On the other hand, members of the Firmicutes phylum, governed by *Lactobacillus iners, Lactobacillus jensenii, Lactobacillus crispatus,* and *Lactobacillus gasser*i inhabit the healthy vagina and also can change their abundance over the time [99]. Pelvic inflammatory disease (PID) occurs when pathogenic bacteria reach the upper genital tract through the cervix and cause uterine (as well as the fallopian tubes and ovaries) inflammation [100]. Study results showed that women with adequate levels of *Lactobacilli species* and a relative abundance of *Mycoplasma hominis, G. Vaginalis, Ureaplasma urealyticum* (To a lesser degree) and Gram-negative anaerobic bacteria were much more potential to develop PID [101]. Furthermore, in the upper genital tract, the chronic inflammatory state caused by PID might cause a dysfunction in the endothelial cells of uterus. Thus, dysfunction of endothelium and chronic inflammation can cause carcinoma [87]. In addition, recent studies have suggested that steroid hormones such as estrogens, and intestinal microbiota may synergize to cause cancer as it has mentioned before [41]. It is worth noting that estrogens including the natural hormones estrone and estradiol, induce different types of tumors in laboratory animals. It is also recognized to be a carcinogen in humans, raising the risk for uterine cancer as well as breast cancer which have discussed previously. Different types of DNA damage were observed as part of the research into the mechanisms of carcinomas induced by hormones which were mediated by estrogen in cell-free systems, in vivo or in cultured cells [102]. There is a relationship between pelvic inflammatory disease and vaginal microbiome and bacterial vaginosis. Thus, microbiome disruption can be considered as an indirect risk factor for endometrial cancer. Similarly, ovarian cancer risk can be improved through the indirect effects of the vaginal microbiome, modulation of local immunosurveillance and regional inflammation. Recently, one study showed that the ovaries and fallopian tubes have a specific microbiome. Compared to the control group without cancer, there were different compositions of microbiomes of upper genital tract in patients with epithelial ovarian cancer. There was also a relationship between the composition of the uterine microbiome and endometrial cancer in a new study. Especially there was a relationship between cancer, *A. vaginae* and *a Porphyromonas* species [90]. The role in oncogenesis is not only limited to bacteria but according to the study of Mileshkin et al. [103], the incidence of cervical cancer among women with HIV is growing. In fact, there is an association between enhanced HPV uterine cervical carcinogenesis and immunosuppression followed by HIV [104]. Microbiomes with high levels of *L. crispatus* were generally related to healthy individuals [105].

Table 2
Association of different vaginal microbiome species with disease development.

Bacteria	Association with HPV	Association with CIN
Lactobacillus iners	–	+
Lactobacillus gasseri	+	–
Atopobium vaginae	+	+
Gardnerella vaginalis	+	+
Fusobacterium	+	+
Sneathia	+	+

On the other hand, *Lactobacillus iners* was related to cervical cancer alone [106] or in combination with HPV infection and a higher degree of cervical intraepithelial neoplasia (CIN) in patients with a positive HPV test [107]. Atopobium vaginae, Gardnerella vaginalis, and Lactobacillus iners may cause the synergistic effect of the risky microbial pattern with HPV infection on the increase of cervical intraepithelial neoplasia risk [107] (Table 2). However, another study showed that there was a relationship between *L. iners* and reduction of squamous intraepithelial lesions risk and cervical cancer [105]. Cervical intraepithelial neoplasia (CIN) was also related to other *Lactobacillus* species in a variable manner. Also there was a relationship between CIN and less abundant bacterial species (*Atopobium vaginae*, *G. vaginalis*, *Fusobacterium*, etc.) [90]. Cytokine profiling has indicated increased interleukin (IL)-4 and TGF-βRI mRNA local levels in *Fusobacterium*-dominated gut microbiomes (Fig. 1, E) [90]. In a similar way, in in patients with squamous intraepithelial lesion microbiomes with high levels of *Sneathia* were observed (Table 2). Diet has a potential impact on the microbiome. A higher rate of CIN observed in women with semi-Western-style diets compared with fish and vegetables rich diets [90]. Moreover, the sex-hormone-the microbiome-immune system will affect women's susceptibility to HIV-1. Serious shifts of hormones can change the proportion of anaerobic bacteria to those influenced by lactobacilli. If the levels of estrogen decrease significantly in menopausal women, *lactobacilli* become less likely in dominating the vaginal microbiome [24].

9. New clinical trials

The ClinicalTrials.gov Web site, is a study database for breast, ovary and endometrium conditions or diseases, a summary of the study protocol, including the purpose of study, status, the number of participants, and outcome measures is shown in (Table 3).

10. Conclusion

Some bacteria are known to affect human health including organisms that are associated with breast, ovarian, and uterine cancers. In regards to cancer development, bacteria are considered to have an important pathogenic role in carcinogenesis through several different mechanism. Additionally, specific bacteria and/or viruses are described as cancer-inducing factors in this review. Despite their potential oncogenic effects, microbiota might be manipulated for the treatment of cancers, so information about the role of the bacteria in cancers requires further investigations. Some female cancers are also diagnosed among HIV-infected individuals which are possible to be associated with the most common sexually transmitted infectious agent, human papillomavirus (HPV) and considered to be a new target to study. Even the link between HIV -or other viruses- and carcinogens via immunosuppression pathways is still limited and requires an extended investigation.

Conflict of interest

None.

Table 3
Summary of a few studies that have addressed the microbiota and related conditions or disease.

Identifier	Condition or disease	Intervention/treatment	Study Type	Outcome Measures	Estimated Enrollment	Observational Model
NCT01461070	Breast Neoplasms		Observational	Breast cancer association Fecal microbiome-systemic estrogen association	175 Participants	Case-Control
NCT03885648	Breast Cancer		Observational	Metagenomic study of mammary and intestinal microbiota	200 Participants	Case-Control
NCT04138979	Microbiota	Cyclophosphamide	Observational	Transcriptional changes in gut microbiota measured by 16S rRNA gene	80 Participants	Case-Control
NCT03586297	Triple Negative Breast Cancer		Observational	Pathologic complete response in triple negative breast cancer patients treated with neoadjuvant chemotherapy related with variability in gut and intratumoral microbiota composition	49 Participants	Cohort
NCT03388996	Benign ovarian disease and Malignant ovarian disease	Diagnostic Test: microbiome 16 s RNA analysis and micro culture of discharges/flushing fluid from vagina, faces and fimbria end of fallopian tube	Observational	Difference of species distribution of microorganism according to 16 s RNA analysis	40 Participants	Case-Control
NCT01549782	Microbiota Endometrial Neoplasms	Dietary Supplement: Inulin and Fructo-oligosaccharide	Interventional (Clinical Trial)	Changes in *Lactobacillus* and *Bifidobacterium* populations	40 Participants	Parallel Assignment
NCT03598946	Neoplasms, Ovarian	Human Papilloma Virus Test urinary	Interventional (Clinical Trial)	Evaluate the rate of participation in the urinary test group	12500 Participants	Single Group Assignment

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