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REVIEW

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Microbiota, a new tool for gynaecological cancer prevention and treatment

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Abstract

Human microbiota is the set of symbiotic microorganisms that coexist with the human organism without damaging it. Human microbiota is a good example of mutualism: cooperation between different types of organisms that brings an advantage to each of them. By "microbiota" we mean the set of actual microorganisms, while the term "microbiome" refers to the genetic heritage of the microbiota. The so-called "intestinal flora" is part of the complex human microbiota. An important function of human microbiota is the breakdown of substances that our system is unable to dismantle, such as cartilage and cellulose molecules. Another important function is the synthesis of indispensable substances, for example vitamin K, which plays an essential role in blood clotting. Human microbiota competes with non-symbiotic bacteria that could replicate in various areas of the body. By "vaginal flora" or "vaginal bacterial flora" we mean the set of microorganisms, mostly of bacterial origin, which colonize the vaginal cavity, and which constitute a form of defense against pathogenic attackers. The quantity and type of bacteria present in the flora has a direct influence on the state of a woman's health. A healthy vaginal flora helps prevent fungal infections (typically candida, the cause of vaginal candidiasis) and other possible pathologies, occupying the resources necessary for their development and metabolism. Flora imbalances can also be caused by hormonal imbalances or disorders, by physical or psychological stress but also by excessive intimate hygiene with unsuitable or too aggressive products. Pathologies connected to microbiota are still the subject of study today, but numerous publications show that an altered composition of microbiota is implicated in psychiatric pathologies (for example, among the most studied we find anxiety disorder), in chronic inflammatory diseases, heart failure, and also in cancer. The aim of this review is to emphasize the importance of microbiota on the incidence, evolution, prevention and treatment of gynecological and breast cancers. We aim to clarify the existence of various "local" microbiota, their close relationship with intestinal microbiota and metabolic conditions connected to it. Also, their impact on oncological pathology, and the real possibility of modulating it (therefore, interfering with oncological history of the patients) through targeted but common clinical practice therapeutic interventions, such as the use of phytotherapeutic compounds, nutraceuticals, probiotics and prebiotics. The intent of this work is, on one hand, to highlight the benefits of a correct diet in prevention and treatment of gynecological neoplasms, on the other hand, to highlight false information, which can cause harm to patients' health.

Keywords

Microbiota; Gynecological cancer; Prevention; Treatment

1. Introduction

The microbiota, also known as "bacterial flora" (a misnomer because the microbiota is made up not only of bacteria, but also of fungi and viruses, and not "plants") represents the set of thousands of billions of microorganisms present in a multicellular living organism. These microorganisms live inside and outside our body located at the intestinal, oral and vaginal mucosal level and work in conditions of symbiosis to perform vital functions, playing an active role in the health of human beings. These microorganisms perform the task of digesting food, absorbing and producing nutrients, and modulating the immune system [1]. The microbiota affects metabolism, immune function, and even mental health. All the microorganisms that populate our body are fundamental modulators of health and disease. Alterations in the microbiota

lead to a condition known as "dysbiosis" and have been associated with various pathologies (gastrointestinal, metabolic, renal, gynecological, cardiological, and oncological), often inflammatory, autoimmune or immune-mediated [2].

The term "microbiota" is commonly confused with the term "microbiome" which instead refers to the set of all genes present in the microbiota, largely more than genes that make up the human genome. The microbiome corresponds to the entire genetic heritage of the microbiota. Research conducted within the "Human Microbiome Project" (HMP) since 2007 have highlighted that this community of microorganisms is made up of several species of bacteria, fungi, viruses, protozoa and helminths that intertwine complex ecological interactions with each other and with our organism [3, 4]. These microorganisms perform many fundamental functions:

- they metabolize fibers and other nutrients, and produce vitamins;
- they are immune system regulators;
- they have a very important role in metabolism ("metabolome");
- they are involved in the production of neuromodulators; and
- numerous other functions that are gradually added to an already large list [5, 6].

Problems of the microbiota can manifest with a variety of symptoms, including gastrointestinal disorders such as diarrhea, constipation, abdominal bloating, changes in body weight and increased susceptibility to infections. The alteration of the composition and above all the diversity of these populations of microorganisms is associated with the onset of pathologies ranging, for example, from autoimmune problems, such as inflammatory bowel diseases (IBD) and rheumatoid arthritis to metabolic diseases (obesity and diabetes), from gynecological pathologies to mood alterations, to name a few. Hundreds of thousands of articles and scientific works almost every day highlight new functions or correlations between alterations of microbiota and human diseases [7]. In recent years, in fact, research aimed at investigating the role of microbiota has multiplied. These studies have made it possible to eliminate the association that has existed for centuries according to which "bacterial" was a synonym for "pathological". However, the scientific community has not yet managed to find a univocal definition of "healthy microbiota", as well as "a healthy microbiota for one person may not be healthy for another". We are now starting to have a first perception of who the actors involved in this scenario are, but there is still much to explore [8].

Generally, we use to talk about microbiota in relation to the intestine. Intestinal microbiota is made up of trillions of microorganisms, yet to be fully characterized in their compositional complexity. It is the most important and powerful among the different communities of microbiota that inhabit our body from the nostrils to respiratory tract, from the mouth to gastrointestinal tract, from the skin to mucous membranes, from the placenta to amniotic fluid, as well as fetal intestine and breast milk. For some years, scientific and medical research has been studying the characteristics and potential inherent in the colonies of microorganisms present in humans. Oncology research is also investigating the links between the microorganisms that live in symbiosis with our body and cancer prevention and treatment. Recent studies, in fact, have shown that microbiota, and particularly the intestinal one, which includes over 70% of the microbes in the human body (approximately 3×10^{13} bacterial cells), has multiple relationships with oncological pathologies. Thanks to its ability to modulate host metabolism, inflammation and immunity, intestinal microbiota is involved in the initiation and/or progression of cancer both at the epithelial barriers and in sterile tissues, including gastric cancer, colon-rectal cancer, hepatocellular carcinoma, pancreatic cancer, melanoma and breast cancer. In fact, when an alteration of the balance in the microbial ecosystem occurs, commensal bacteria, called "pathobionts", can expand and acquire pathogenic characteristics by increasing the production of pro-inflammatory mediators and creating an environment that favors the proliferation of cancer cells [9].

The field of microbiology research in oncology has proven to be interesting and important. This is why the International Cancer Microbiome Consortium (ICMC) was founded in 2017, with the aim of promoting research on microbiome in oncology, creating expert consensus documents on the topic and providing educational tools both for those involved in oncology research and for those who deal with cancer every day as a clinician [10, 11]. A very complex topic, which does not lend itself to being studied with a microscope. Techniques for studying the composition and function of the microbiome are becoming more refined every day. The basic structure of normal microbiome in an adult individual has now been defined. However, this can be expressed in many different variables influenced by diet, ethnicity, structure genetics of the host, age and medications taken. For this reason, today we resort to the study of the deoxy-ribonucleic acid (DNA) of the microbiome and to the so-called "omics" technologies, which have made it possible to create large databases on the subject. Even so, it is necessary to bring together the data of different research groups, to create international consortia to work on big data, which can only be interpreted through artificial intelligence (AI) tools, such as machine learning (ML), deep learning (DL), neural networks (NN), *etc*. Microbiota profiling, through AI, will soon influence prevention, early diagnosis, and therapy for cancer and many other diseases. Moreover, this will lead to using the microorganisms with which we live both as a biomarker of various pathologies and as a therapeutic target, included in a broader treatment strategy. A well-balanced microbiome carries out a series of fundamental tasks for maintaining health. Usually, however, we realize the existence of these microorganisms when the balance of this delicate coexistence breaks down, as happens in the case of IBD, metabolic syndrome and obesity, antibiotic-induced diarrhea, neurological disorders, cardiovascular diseases (CVD) [12, 13] and cancer. It is in this way that scientists have discovered that the composition of microbiome can influence the appearance of cancer and response to therapies. In addition, this leads us to predict that soon microbiota profiling will enter the treatment project for cancer patients, acting both as a biomarker and as a therapeutic target [14].

In gynecology, one of the main fields of interest of the last ten years has been the study of the correlation between alterations in cervical-vaginal microbiota and a wide spectrum

of female pathologies. There is data in the literature showing that an unfavorable microbiota is responsible for many gynecological conditions, including idiopathic infertility, preterm birth, spontaneous abortions and cancer. In addition, extravaginal districts such as the uterus, tubes and ovaries have their own specific microbiota: the presence of Lactobacilli is fundamental to keeping disease development under control, as we will see [15]. Our aim is to emphasize the importance of microbiota on the incidence, evolution, prevention and treatment of gynecological and breast cancers. We aim to clarify the existence of various "local" microbiota, their close relationship with intestinal microbiota and metabolic conditions connected to it. Also, their impact on oncological pathology, and the real possibility of modulating it (therefore, interfering with oncological history of the patients) through targeted but common clinical practice therapeutic interventions, such as the use of phytotherapeutic compounds, nutraceuticals, probiotics and prebiotics. This could be a first and decisive boost towards recognition of new aspects of gynecological and breast oncological pathology and to provide new possible weapons, not alternatives but complementary, to be added to preventive and therapeutics currently in use to expand and improve our ability to control the pathology in question. Nutrition and cancer are a topic that in recent times has gained much relevance both in the media and in the scientific community. The intent of this work is, on one hand, to highlight the benefits of a correct diet in prevention and treatment of gynecological neoplasms, on the other hand, to highlight false information, which can cause harm to patients' health [16–20].

2. Pathophysiology of the female genital and breast microbiota

Interest in human microbiota has recently expanded beyond the gut to include many other organs in which microorganisms may have health implications. We are made up of 99% bacteria and less than 1% of ourselves [21]. Bacteria are everywhere, with different microbiota for different parts of the body:

- the skin, for example, is the kingdom of Propionibacterium, Corynebacterium and Staphylococcus;
- Bacteroides, on the other hand, live in the intestine;
- Streptococcus is found in the mouth; and
- the vagina is the kingdom of Lactobacillus: but Lactobacilli are not all the same, as we will say below.

Lactobacillus crispatus (*L. crispatus*)-dominant vaginal microbiota is the backbone of vaginal defense system. And it is for this reason that *L. crispatus*, which identifies the community state type (CST)-I vaginotype, as we will see below, receives the greatest consensus from the scientific world. In fact, it appears to be the one that more than others guarantee against risk of gynecological infections, those due to:

- bacteria (Chlamydia, Gardnerella and Mycoplasma);
- protozoa (Trichomonas);
- fungi (Candida); and
- viruses (Human Papilloma Virus (HPV) and Herpes Simplex Virus (HSV)).

Human microbiota is also a "multi-endocrine" gland:

- it produces and secretes hormones:
  - estrogens, with the group of bacteria called "estrobolome" (see below); and
  - testosterone and other androgens, with the bacteria defined as "androbolome";
- it responds to hormones produced by the woman's or man's body and to hormonal therapies, for example to contraceptive pills or hormone replacement therapies (HRT), but also to insulin or thyroid hormones; and
- it regulates the levels of hormones that flow in the blood.

Recent studies suggest that gut microbes also play a crucial role in regulating levels of circulating estrogens, which regulate fat mass and adipocyte differentiation, female reproductive health function, cardiovascular health, bone turnover and cell replication [22]. Estrobolome, the aggregate of enteric bacterial genes whose products are capable of metabolizing estrogens, acts on conjugated estrogens and estrogen metabolites with downstream physiological effects. Estrogens are produced primarily in the ovaries, adrenal glands and adipose tissue and circulate in the bloodstream in free or protein-bound form after being metabolized by the liver, where estrogens and their metabolites excreted in the bile come from. Estrobolome produces an enzyme, beta-glucuronidase, which deconjugates estrogens in their active form, making them free and available to bind to estrogen receptors (ESR), influencing estrogen-dependent physiological processes. An estrobolome enriched in genes encoding enzymes favoring deconjugation promotes re-absorption of free estrogens that contribute to the host's total estrogen burden. An alteration of estrobolome and its regulatory functions leads to an imbalance of all the just listed functions, promoting the onset of chronic pathologies. What alters the balance of intestinal microbiome can alter estrobolome:

- diet;
- lifestyle;
- inappropriate use of medications and antibiotics;
- endocrine dis-regulators: pesticides, toxic residues in plastic and genetically modified organisms (GMO); and
- consumption of phytoestrogens (soya): phytoestrogens may play an estrogenic and/or anti-estrogenic role.

Estrobolome could be the mediator of such effects on endogenous estrogens.

Microbiota of the female reproductive tract (FRT) is divided into two categories: those of the low and those of the high FRT. Those of the high FRT represent an evolution of those below, *i.e.*, the vagina and cervix, and only recently has their presence and nature been recognized. They have a biomass about 10,000 times smaller and a greater biodiversity, in which the Lactobacilli quota, from 97–100% in the vagina, tends to be reduced to 30% in the endometrium up to 1.7–2% in the Fallopian tubes and ovaries. Vaginal microbiota composition is conditioned by estrogen levels: in the prepubertal phase, there are low levels of estrogen, a thin mucosal layer, little glycogen, few Lactobacilli and high potential of hydrogen (pH). In puberty, under estrogen control, vaginal epithelium thickens and the increase in glycogen selects fermenting microorganisms. At this point, vaginal microbiota is dominated by Lactobacilli, especially *L. crispatus*, *L. gasseri*, *L. iners* and *L. jensenii*. Glycogen is metabolized by these Lactobacilli into lactic acid and hydrogen peroxide (H_2O_2), decreasing pH and

therefore hindering proliferation of other bacteria, constituting a defense mechanism. Lactobacilli (over 60 species) represent the majority of lactacid bacteria (LAB), that is, those capable of converting sugars into lactic acid, a property shared with bifid bacteria. Lactobacilli are very concentrated at the vaginal level, a district in which low biodiversity is indicative of tissue health, unlike the intestine. Natural protection, therefore, ideal for counteracting the proliferation of pathogenic microorganisms also thanks to lactic acid production, which brings pH to its physiological values (3.5–4.5). In addition, this task alone constitutes a powerful barrier in defense of intimate health. Today, we understand that the ability to "read" the microbiota enables the identification of risk factors for various diseases: from HPV to infertility, from atrophic vulvovaginitis to preterm birth. It is no coincidence then that typical gynecological problems have been linked to the fact that this bacterium is present in only 25–40% of women. Then, there is the fact that vaginal microbiota changes throughout a woman's life: as menopause approaches (perimenopause), for example, vaginal microbiota changes and becomes absent precisely from *L. crispatus* [23].

As we have said, intestinal microbiota is considered healthy when it is characterized by richness and diversity of microorganisms, as it has more tools in the "toolbox" to resist and fight external threats, while for vaginal microbiota the question is different, as we speak of "eubiosis" when this is dominated by a single bacterial species. When the imbalance of bacterial composition becomes excessive and chronic, the condition is called "dysbiosis". Dysbiosis is the imbalance of the different populations of bacteria, with decrease in Lactobacilli that act as defense mechanism and with increase in other types of bacteria leading to infections. Dysbiosis in gynecology concerns the intestine-vagina axis and the so-called "double approach", *i.e.*, acting both locally with specific prebiotics and intestinally, to solve gynecological problems. Bacterial and non-bacterial species have demonstrated clinical activity in this sense.

Five types of vaginal microbiota are defined, each characterized by the prevalence of specific bacterial communities, and in particular different species of Lactobacillus. The only exception is represented by the CST-IV type, in which strictly anaerobic and pathogenic bacteria prevail, including Prevotella, Gardnerella, Megasphera and Sneathia. The transition from type III microbiota, characterized by the prevalence of *L. iners*, to type IV microbiota, suggests the role of this bacterium in promoting growth of anaerobic and pathobiont bacteria. Homeostasis of vaginal ecosystem is the result of complex interactions and synergies between the host and various microorganisms that colonize vaginal mucosa. The maintenance of a high number of resident Lactobacilli is a sign of good health condition of the woman. Vaginal microbiota composition, particularly the prevalence of *L. acidophilus*, is influenced by several factors:

- genetic/ethnic (for example, a greater presence of acidophilic Lactobacilli is observed in Caucasian and Asian women);
- physiological: pregnancy, puerperium and menopause;
- hormonal: estrogens increase glycogen in vaginal secretions and thus favor colonization by acidophilic Lactobacilli, which use it to produce lactic acid;
- hygiene habits: use of vaginal irrigations is more frequently associated with dysbiosis and reduction of acidophilic Lactobacilli;
- frequent sexual intercourse (spermatozoa have pH >7); and
- abundant and frequent cycles (cause of rise in pH).

The importance of vaginal microbiota is now evident to the scientific community, given its involvement in various pathological conditions of the FRT. The most common vaginal infections, candidiasis and bacterial vaginosis, and HPV infections are not just simply due to a pathogenic microorganism, but are the result of a more structured dysbiosis at the vaginal level. *L. crispatus* is associated with:

- reduced onset of vaginal infections of both bacterial origin (Gardnerella and Chlamydia) and other etiologies (Candida and *Trichomonas vaginalis*);
- stable condition for vaginal microbiota; and
- state of general well-being during all stages of a woman's life, from puberty to menopause.

Vaginal microbiota has a possible impact also on the pathogenesis of the most common gynecological cancers. While on the one hand vaginal dysbiosis can be associated with the development of cervical cancer, as well as endometrial and ovarian cancer, on the other hand anti-cancer therapies very often cause dysbiosis, both vaginal and intestinal, contributing to many of the side effects of the same therapies. The literature demonstrates the effectiveness of the use of probiotics for the prevention and effectiveness of therapy in gynecological oncology. From a psycho-neuro-endocrine-immunology (PNEI) perspective, it must however be kept in mind that nutrition as a whole and stress management remain two fundamental pillars on which to act also to maintain homeostasis of commensal microorganisms, which can thus prove to be unexpected "friends" of female health, as we have said before. The quantity and quality of lactic acid and the amount of H_2O_2 and bacteriocins produced by these *Lactobacilli species (spp.)* are among the most protective elements against bacterial and HPV infections, and for the latter towards its persistence and consequent precancerous and cancerous lesions on it. Restoration of CST-I is obviously favorable in case of all these pathologies. LAB at the vaginal and intestinal levels are protective in general against cancer, by virtue of their immunostimulatory, pro-apoptotic and antioxidant activities towards reactive oxygen species (ROS) [24].

An interesting area of scientific research is exploring the correlation between microbiota health, HPV infection and cervical cancer. Various research has shown that vaginal microbiota composition plays a fundamental role in susceptibility to HPV infections and persistence and regression of HPV and its associated pathology, *e.g.*, the promotion of uterine cervical intraepithelial neoplasia (CIN). This is so important that, in case of HPV positivity, if vaginal microbiota is dominated by *L. crispatus*, it is more likely that the infection will become negative [25].

HPV infection is widely spread in sexually active women (around 80%) up to the age of 50. In about 90% of cases, the infection tends to resolve through spontaneous viral clearance within a year, while persistence represents an important cause of cervical precancerous or cancerous lesions and a risk factor

for cervical carcinogenesis and oncogenic evolution. Recent evidence supports the hypothesis that alteration of vaginal microbiota, characterized by depletion of acidophilic Lactobacilli and proliferation of other species, is the basis of the acquisition of HPV infection (more than double the risk, regardless of vaccination coverage and age), its persistence, and neoplastic evolution through strengthening of HPV infection [26].

L. acidophilus contributes to the maintenance of eubiosis and protective barrier function of cervical epithelium, preventing the entry of HPV into cervical keratinocytes and counteracting persistence of the infection, through various mechanisms:

- maintenance of acidic pH (3.8–4.5);
- production of antimicrobial substances: H_2O_2 and bacteriocins; and
- local immune system modulation.

There is a direct link between HPV clearance and *Lactobacillus spp.* level. The normal presence of vaginal microbiota hinders the development of bacteria and hence some of their carcinogenic products. Also, the growing role of Pembrolizumab in cervical cancer therapy, should take into account the interesting interplay between immunotherapy and microbiome known effects on the immune system.

Some studies have shown that dysbiosis, with proliferation of pathogenic bacterial species, such as those responsible for bacterial vaginosis (*e.g.*, *Gardnerella vaginalis*), could favor viral replication cycle, persistence of HPV infection, and neoplastic transformation. Dysbiosis is also associated with:

- reduction in cervical mucus production, which has an important function in hindering entry of pathogens;
- increase in pro-inflammatory cytokines, known factors implicated in carcinogenesis; and
- higher levels of oxidative stress, with excessive production of ROS, which cause breakage of DNA double helix, both of HPV episome and host genome, favoring HPV integration into the host genome.

Some researchers suggest that HPV itself could contribute to changes in the stability and composition of vaginal microbiota. Data show that biodiversity is significantly lower in HPV negative women than in HPV positive patients, suggesting that a simplified microbiota, dominated by *Lactobacillus species* (*spp.*), is mostly compatible with the state of physiological balance (*e.g.*, maintenance of pH) which guarantees a correct state of commensalism in childbearing age. Prevalence of *Lactobacillus spp.* (53%) correlates with protection from HPV infection. From these data, two threshold values related to the absence of infection, or its recovery emerge: Lactobacillus 75% and Bifidobacterius 6%. Furthermore, in the group of patients with persistent infection, it is possible to detect a relative abundance (range 5–27%) of potentially pathogenic species such as Gardnerella, Prevotella and *Escherichia coli* (*E. coli*)/Shigella. Further statistical investigations are necessary to verify microbiome patterns significantly associated with persistence of HPV infection [27].

Recent meta-analyses have confirmed how dysbiosis at the vaginal level represents a significant risk factor both for the acquisition of HPV, for its persistence at the cervical-vaginal level, and for progression into dysplastic lesions and invasive carcinomas. The problem, however, is that we must try to understand through clinical as well as preclinical studies what is meant by dysbiosis and the risk of acquiring HPV. "Dysbiosis", in fact, is a very vague term. It may mean reduction in Lactobacilli flora, increase in vaginal pH, increase in other aerobic or anaerobic microorganisms that do not produce lactic acid, and may indicate bacterial vaginosis. "Bacterial vaginosis" is defined as a condition in which CST-IV type bacterial composition prevails. This condition could facilitate persistence of HPV infection and its consequent pathological course. Therefore, a series of different clinical forms that can facilitate acquisition and progression of HPV, to which are added the so-called "co-infectious events", for example *Chlamydia trachomatis*, which could represent a predisposing and favoring factor both for acquisition and for progression of the virus [28–32].

Observational research conducted in Korea on a cohort of 912 women examined the relationship between persistent HPV infection and bacterial vaginosis. The results of this study highlighted a significant difference in vaginal bacterial composition between HPV-positive and non-HPV-positive twin sisters. In HPV-positive women, vaginal microbiota was characterized by lower levels of Lactobacillus and greater pathogenic microbiota diversity. From this research, a line of scientific interest arose for the study of the impact of vaginal microbiota on various gynecological and obstetric pathologies [33]. Similar results were published by a group of American researchers. Their study analyzed vaginal microbiota in a cohort of 32 women. The presence of type IV pathogenic microbiota was in this case clearly associated with HPV positivity. The same scientists also suggest the potential protective role of bacterial species prevalent in CST-II type microbiota, *L. gasseri*, against rapid remission from HPV infection. However, further longitudinal studies are needed to clarify the biological mechanism underlying this relationship [34].

An interesting starting point for further study comes from an Italian project, whose preliminary results seem to confirm previous scientific observations. A group of researchers has in fact analyzed vaginal microbiota of a cohort of 80 women diagnosed with CIN2 and CIN3 type lesions of the uterine cervix related to HPV infection before and after treatment by surgical excision. The patients included in this study were characterized by the prevalence of CST-IV type vaginal microbiota. Furthermore, comparison of vaginal microbiota before and after treatment with surgical excision demonstrated restoration of a healthy vaginal microbiota, with prevalence of the Lactobacillus bacterial genus. On the contrary, women with persistent HPV infection had a much more diverse and potentially pathogenic vaginal microbiota. At the same time, analysis of the inflammatory state at the vaginal level revealed decrease in inflammatory cytokines in patients who experienced remission of HPV inflammation after surgical treatment [35].

The presence of bacterial vaginosis and the increased concentration of anaerobic microorganisms could facilitate HPV presence, persistence, and progression due to deficiency of the host's immune response. Maintaining the correct vaginal bacterial ecosystem protects against risk of contracting HPV. However, vaccination against HPV remains the most useful indication for eradicating cervical cancer. Recently, increasing

evidence has suggested interaction between HPV, cervical-vaginal microenvironment (CVM) condition, and cervical cancer progression. A review aimed to comprehensively investigate the relationship between CVM and HPV infection in the carcinogenesis of cervical cancer and above all to update current research on bacteriotherapy in cervical cancer. HPV infection can induce changes in the CVM. Consequently, this can lead to dysbiosis and CVM cancer. On the other hand, abnormalities in cervical-vaginal microbiota can modify vaginal pH, favor bacteriocins release by pathogenic bacteria, and thus damage the mucous layer. In most healthy women, CVM is dominated by *Lactobacillus spp*., which benefits the host through symbiotic relationships. The absence or poor presence of *Lactobacillus spp*. induces dysbiosis of CVM, which can favor the development of cancer through different mechanisms, such as promotion of chronic inflammation, immune system dysregulation and production of genotoxins. Consequently, such dysbiosis may contribute to HPV-related cervical cancer by interfering with HPV infection, binding, internalization, integration, gene expression and telomerase activation [36].

Lactobacilli play a fundamental role in women's cervical-vaginal health: they protect the vagina from bacterial invasion by maintaining an acidic environment and promoting integrity of the epithelial cellular barrier and intercellular junctional proteins. Most studies revealed a decrease in *Lactobacillus spp*. and an increase in CMV biodiversity in high-risk HPV-positive women compared to high-risk HPV-negative women. Specifically, the dominant presence of *L. crispatus* tends to enhance CMV protection through production of antimicrobial metabolites, decrease in glucose, and production of phenyllactate and N-acetylated amino acids. Furthermore, various studies have identified a high abundance of *L. crispatus* in low-risk CIN, while *L. iners* was dominant in medium-risk CIN.

The last decade has seen rapid development of the use of lactobacillary-type probiotics in cervical cancer, starting from the hypothesis that they could promote apoptosis and inhibit proliferation and metastasis of cancer cells. It has been shown that probiotics can be used as an adjunctive agent for enhancement or modulation of other diagnostic and therapeutic methods. Furthermore, it has come to be understood that Lactobacilli can increase HPV elimination through three mechanisms. First, an increased number of probiotic strains in the vagina can prevent and reduce HPV infections by competing for space or nutrition and releasing several inhibitory factors, such as lactic acid, bacteriocins, biosurfactants and aggregation molecules. Secondly, promoting immune response is the main mechanism against viral infections. Finally, the direct elimination of viruses can occur through secretion of specific metabolites. Among the various studies carried out in this regard, it was observed that HPV-positive women who took the long-term probiotic oral *L. crispatus* had HPV-related cytological abnormalities significantly reduced compared to control group. An increase in HPV clearance has also been reported after 90 days of *L. crispatus* intake. Furthermore, in some cases, *L. crispatus* has become the dominant species in cervical-vaginal microbiota. Further studies on the relationship between vaginal microbiota and HPV infection could be useful to understand how to maintain eubiosis and make prevention and treatment of HPV-related lesions more effective [37, 38].

Probiotics, therefore, are slowly demonstrating that they can offer new opportunities for future therapies and could change response to cancer treatment, although well-designed studies on anticancer function of probiotics in the management of patients with cervical cancer need to be developed. Less known, in fact, is their relationship with the response to platinum-based chemotherapy. Although chemotherapy and surgery have demonstrated good efficacy in non-metastatic patients, they do not always achieve the desired success. It is therefore important to understand the dynamics that can justify a non-response, which should hopefully be identified in the early stages of the pathology. Alterations in the vaginal microbiota in patients with cervical cancer could provide information for the outcome of platinum-based chemotherapy. A study analyzed vaginal microbiota diversity in women with advanced non-metastatic cervical cancer, comparing the characteristics with those of healthy women and based on response to therapy. Alpha diversity and abundance of Bacteroides appeared to be related to resistance in the early stages. Women with cervical cancer have a peculiar local microbiota profile based on their response to platinum-based chemotherapy. Monitoring alpha diversity and abundance of Bacteroides could therefore represent a valid tool for early identification of cases of therapeutic ineffectiveness. Given the confirmed involvement of local microorganisms in the etiopathogenesis and course of cervical cancer, microbiota monitoring could represent a valid diagnosis and/or prevention strategy. To summarize, therefore, vaginal microbiota profile is altered not only by the presence of cervical cancer, but it would also appear to be able to provide valuable information for the outcome of platinum-based chemotherapy [39, 40]. These are very promising results, firstly regarding confirmation of the fundamental role played by vaginal microbiota in creating a microenvironment favorable to preneoplastic lesion's pathogenesis. Secondly, regarding the potential therapeutic role of certain bacterial communities, such as some *Lactobacillus spp*. However, further insights into the underlying mechanisms for optimization of targeted interventions are necessary.

The same can be said of the recently discovered endometrial microbiota, whose Lactobacilli flora is of intestinal, blood, and vaginal ascending derivation: many studies correlate its Lactobacilli content positively with better reproductive capacity and good success of an embryonic implant [41]. The uterus is not a sterile environment: bacterial forms have been isolated within the uterus since the 1990s [42]. In 2017, a work demonstrated that there is a continuum of microbiota along the female genital tract from the vagina to the uterus, confirming a non-sterile environment [43, 44]. Microbiota of the vagina and endometrium are very similar but not identical. The most plausible way for colonization of the upper genital tract is the transmigration of bacteria from the vagina, intestine, and mouth. Vaginal and endometrial microbiota are mainly dominated by Lactobacilli in different proportions [45].

An intrauterine microbiota rich in Lactobacilli is positively correlated with a lower risk of endometrial polyps but also endometrial cancer, given that they depend on bacteria of pro-inflammatory vaginal derivation (Atopobium and Porphyromonas) poorly represented in CST-I vaginotypes, rich in *L.*

crispatus and with low pH. Studies on endometrial cancer have led to several well-defined genetic and risk factors but mechanically unconnected environments. Microbiome is one of the emerging modulators between environmental triggers and genetic expression. Investigations into the composition of uterine microbiome have revealed its putative role in endometrial cancer. Several significantly enriched taxa were found in samples belonging to the endometrial cancer cohort: Firmicutes (Anaerostipes, ph2, Dialister, Peptoniphilus, 1-68, Ruminococcus and Anaerotruncus), Spirochetes (Treponema), Actinobacteria (Atopobium), Bacteroidetes (Bacteroids and Porphyromonas), and Proteobacteria (Artrorospira). Nevertheless, the simultaneous vaginal presence of Atopobium, *Porphyromonas somerae* (99%), and elevated vaginal pH (>4.5) were found associated with disease status. These findings, given the documented association of the identified microorganisms with other pathologies, suggest the possibility of microbiome role in the manifestation, etiology, or progression of endometrial cancer that should be further studied [46].

The association between ovarian cancer and the pathogens responsible for it has recently been discovered and, since there are many pathogens, it is difficult to establish which ones are those most implicated but Cytomegalovirus (CMV), Chlamydia, Acinetobacter, and Proteobacteria seem all to have a role. There are therefore many microbial entities potentially co-responsible for ovarian cancer. We could stick to the concept of general dysbiosis rather than a real one and truly pathogenic and it wouldn't surprise if in the evolution of this discussion in the coming years the importance of HPV would be increasingly evident, also with regards to ovarian cancer and not just cervical cancer. It is well established that ovarian cancer is related to risk factors such as genetic mutations, reproductive history, and exogenous hormones. A condition of vaginal dysbiosis was also found to be present in its pathogenesis and progression, as well as appearing to underlie complications of anti-cancer therapy. Microbiome alteration could affect all ovarian cancer histotypes [47].

The characteristics of ovarian cancer microbiome provide information for the development of targeted therapies against ovarian cancer [48]. The correlation between intestinal dysbiosis and ovarian cancer has only been demonstrated in mouse models. There are currently no studies characterizing the composition of gut microbiome in women with ovarian cancer and analyzing variations of the latter during the various phases of treatments (surgery and chemotherapy) and during follow-up. Such a study should evaluate the variation of intestinal microbiota in the various phases of ovarian cancer's history through the collection of fecal samples from patients during treatment and follow-up phases.

A 2019 work demonstrated for the first time an association between cervical-vaginal microbiota, breast cancer (BRCA)1 mutation status, and ovarian cancer risk. Of BRCA1 gene patients, 45–60% (versus 10% of the general population) develop breast cancer and 20–40% (compared to about 1–2% of the general population) develop ovarian cancer during their lifetime. The risk of BRCA2 gene patients is 25–40% of developing breast cancer and 10–20% of developing ovarian cancer in their lifetime. The study has considered one group of women with ovarian cancer and another with BRCA mutation. Their CST were divided into an L type (>50% in Lactobacilli) and an O type (<50%). The first thing observed was that type O was more represented in menopause and less in fertile age, which was also expected due to the lack/deficiency of estrogenic boost. More interesting was the positive correlation between ovarian type O, cancer and mutation, as well as ovarian cancer risk and the presence of the mutation were higher for type O. The conclusion was that having a type O CST, therefore with fewer Lactobacilli, was positively correlated with the presence of ovarian cancer and BRCA mutation, even more so if the woman was of advanced age. The researchers therefore wondered whether integration of Lactobacilli and estrogen could be preventive of ovarian cancer onset, especially in those women with mutation who do not intend to have preventive surgery [49].

Another 2019 study showed that the ratio Proteobacteria/Firmicutes was significantly increased in women with ovarian cancer, where the mainly increased Proteobacter was Acinetobacter and the decreased Firmicutes were the Lactobacilli [50]. The existence of a microbial continuum along the female genital tract has been demonstrated: the direct transfer of vaginal microbes upwards could mediate the influences of vaginal microbiota on the upper genital tract, thus explaining the correlation of vaginal dysbiosis with endometriosis, Pelvic Inflammatory Disease (PID) and endometrial and cervical cancer [51, 52]. Previous studies have revealed that PID or endometriosis could predispose to ovarian cancer onset. With the growing recognition of the role of inflammation in ovarian cancer carcinogenesis, pro-inflammatory microbial components might participate to cancer progression through the induction of inflammation-related signaling pathways. In fact, it has been demonstrated that bacterial-derived molecules such as lipopolysaccharide isolated from *E. coli* can induce the production of pro-inflammatory cytokines in already present ovarian cancer cells, thus promoting cancer growth also through the stimulation of Toll-Like Receptors (TLR), also favoring the development of chemoresistance.

Growing evidence has revealed potential correlations between microbiota and achieving therapeutic efficacy during chemotherapy for ovarian cancer. For example, in over 30% of patients with primary ovarian cancer resistant to cis-platinum, an alteration in the dominance of vaginal microbiota, which changed from Lactobacillus to Escherichia, was present. Moreover, from examination of the composition of vaginal microbiota and immune checkpoint proteins, a positive correlation is observed between *L. crispatus* levels and the regulation of anti-cancer immunity [53].

A review analyzed the strategies for manipulating vaginal microbiota to reconstitute its optimal composition and to exploit the special characteristics of specific bacterial strains involved in ovarian cancer treatment to obtain adjuvant therapeutic effects. Vaginal microbiota transplantation is giving excellent results, based on fecal material transplant, as a new treatment strategy for both endometriosis and other infectious diseases, as well as in management of ovarian cancer therapy and related post-therapy complications [54]. Another review summarized the potential role of vaginal microbiota in both management of ovarian cancer therapy and treatment of related

complications, as well as also proposing potential support strategies such as use of probiotic supplements and use of vaginal microbiota transplantation [55]. Probiotic integration with a particular strain of *L. crispatus* has also proven useful in preventing recurrence of bacterial vaginosis, counteracting dysbiosis through reconstitution of vaginal colonization of *L. crispatus*, thus permanently reducing the abundance of genera associated with bacterial vaginosis such as *Prevotella spp.* and *Megasphaera spp.*, and generally normalizing all the possible pro-inflammatory and carcinogenic effects. Due to the great potential of this strategy, it is necessary to further explore the therapeutic effects of vaginal microbiota modulation, to exploit the advantages of vaginal probiotics in ovarian cancer treatment [56].

The breast has its own microbiota, strictly individual and largely related to the intestinal one, which is much better known, through an intestine-breast axis, which is still being studied. There is already important evidence that breast tissue dysbiosis can predispose to inflammation and therefore to cancer transformation, in analogy with what happens in intestinal cancer. This new frontier of oncology, defined as "oncobiotics", is opening new scenarios in understanding breast cancer pathogenesis and could have important implications in the fight against it.

Data from a case-control study suggests that intestinal microbiota composition can influence the risk of developing breast cancer, regardless of circulating estrogen levels [57]. In this study, post-menopausal women with a recent diagnosis of breast cancer had a gut microbiota that contained fewer bacterial species than that of similar women without breast cancer. Additionally, women with breast cancer had higher concentrations of Clostridiaceae, Faecalibacterium and Ruminococcaceae, and lower levels of Dorea and Lachnospiraceae.

Alcohol stimulates the production of estrogens and androgens circulating in the blood, important hormones in breast tissue growth and development. If such hormones are in excess, the risk of cancer increases. Estrogens act like signaling molecules through different pathways, including canonical pathways (alpha and beta-receptors) and non-canonical mechanisms. ESR are widely distributed in tissues. Estrogen circulates freely and is bound to proteins. As we have said before, in the liver, estrogens undergo estradiol (E2) and estrone (E1) interconversion and first-pass metabolism. There, estrogen hepatic conjugation allows biliary excretion of conjugated estrogens and conjugated estrogen metabolites in the gastro-intestinal tract in which beta-glucuronidase, glucosidase, and hydroxysteroid dehydrogenase of bacterial origin (the estrobolome fraction of microbiome) regenerate "free" forms of these molecules. Enterohepatic circulation, therefore, contributes to plasma levels of estrogens and their metabolites. An estrobolome enriched with bacteria whose enzyme activity is higher in deconjugation and hydroxylating functions would lead to greater relative levels of free circulating estrogen. Lactobacilli administered by mouth to some women are then found in the breast tissue, intent on exercising an anti-cancer function.

Intestinal microbiome alteration in tissues such as endometrium and breast could increase beta-glucuronidase activity and therefore free and active estrogens levels, which, by binding to receptors, would promote cellular proliferation of those tissues sensitive to estrogenic activity. Intestinal eubiosis can positively influence microbiota of tissues such as endometrium, breast and ovary. Intestinal Lactobacilli could reach tissues and explicate an anti-carcinogenic action. In breast cancer, an alteration of intestinal microbiota often occurs. Higher abundance of *Sellimonas spp.* predicted a higher risk of ESR-positive breast cancer, with a direct effect on breast cancer. The harmful effect of Sellimonas is a direct effect, *i.e.*, independent of common risk factors for breast cancer such as menopause, body mass index (BMI), weekly consumption of alcoholic beverages, and smoking. It was reported that Sellimonas was overrepresented in fecal samples from patients with more aggressive cancer, suggesting a potential carcinogenic role of Sellimonas in human hosts. However, the underlying mechanism is not yet well elucidated [58].

Since the presence of Lactobacilli is closely related to the presence of estrogen, and having estrogen means having Lactobacilli producing lactic acid and a low pH, it's intuitive that a woman who has had breast cancer is comparable to a woman that has gone through menopause because she is taking aromatase inhibitors, and she no longer has circulating hormones. This hormonal decrease, which is obviously a good thing for breast cancer, becomes negative at a gynecological level, as estrogen reduction leads the patient to have fewer Lactobacilli in the vagina and potentially more unfavorable CST. Now, it is equally obvious that in this patient we cannot restore the estrogenic quota as she is taking aromatase inhibitors, and it would be a dangerous contradiction for her breast. Therefore, we should intervene by bringing it back to a favorable CST without increasing hormones. For what concerns tamoxifen (TMX), the relationship between the presence of a certain type of biodiversity at the vaginal level with the production of polyps is unequivocal. Since we know that one of the most important problems of TMX is precisely the formation of polyps and the risk of endometrial cancer, changing microbiota could also mean decreasing the possibility that a woman taking TMX produces polyps and potentially endometrial cancer [59].

In recent research, the triple negative form (ESR−, progesterone receptor (PR)−, human epidermal growth factor receptor 2 (HER2)−), which still often has an unfavorable prognosis, and the Luminal A subtype (ER+, PR+, Kiel 67 (Ki67) <20, HER2−), characterized instead by a favorable prognosis, have been examined. The study focused on changes in the diversity of breast microbiome. The Luminal-A subtype and the triple negative could have differences both in bacterial community composition and in genome. Luminal-A had higher species diversity and abundance of Sphingomonadaceae, which are associated with healthy breast tissue and better clinical outcomes, while triple-negative breast cancer had lower species diversity and abundance of Pseudomonas and Neisseriaceae, which have been associated with breast cancer survival and cell growth [60]. In this work, an extremely relevant fact is confirmed: composition of the bacterial populations that colonize breast tissue differs in a statistically significant manner between hormone-sensitive cancers with a more favorable prognosis (Luminal A) and triple-negative cancers, with a more aggressive clinical behavior. In particular, the study

highlights that microbial biodiversity is significantly greater in less aggressive cancers, confirming what is already present in previous works. Obviously, the present study is not able to demonstrate whether this different biodiversity precedes cancer transformation or is a consequence of it, but some data also highlighted by a study would seem to indicate breast tissue dysbiosis as a contributory cause of carcinogenesis [61].

The good news is that this altered bacterial composition depends largely on our behaviors and therefore can be corrected through healthy lifestyles: a demonstrated positive role on microbial diversity or "eubiosis" is in fact played by a varied diet, predominantly but not exclusively plant-based, integral, by physical exercise, and moderate consumption of drugs, in particular antibiotics. New research shows that acting on the microorganisms that live in our intestine could lead to important results ranging from prevention to improved therapies, illustrating the protective action carried out by intestinal microbiota metabolites against breast cancer [62]. Numerous studies agree in confirming the protective action against breast cancer by:

- short-chain fatty acids, such as butyrate;
- nisin, a bacteriocin produced by the bacterium *Lactococcus lactis*, which also prevents various forms of gastrointestinal cancer; and
- inosine, a naturally occurring purine nucleoside formed by the deamination of adenosine, has demonstrated several noteworthy properties in experimental studies; these properties span neurological, immunological, and metabolic domains.

Researchers confirm that diet affects breast cancer and correct eating habits prevent disease and relapses [63]. This was also demonstrated by a large study which involved 49 thousand post-menopausal women between the ages of 50 and 79, with no history of breast cancer. The researchers divided the women into two groups: the first had to continue following their diet in which fat represented 32% or more of daily calories. The second group, however, had to adopt a diet that aimed to reduce fat consumption, until it reached 20% or less of caloric intake, plus at least one portion of vegetables, fruit, and cereals per day. Overall, women who followed the balanced low-fat diet showed health benefits, with a 21% reduction in the risk of death from breast cancer [64].

A healthy diet therefore plays an important role in breast cancer prevention, and brings with it undeniable benefits, which reduce other risk factors: loss of weight, a greater desire to practice regular physical movement, and substantial decrease in consumption of alcoholic beverages. Losing weight leads to a significant decrease in visceral fat, which, when present, contributes to creating a general inflammatory state and high levels of insulin and glucose. To dissolve fat, therefore, diet must be rich in whole grains, vegetables, and legumes. In addition, animal fats must be limited because they tend to slow down insulin action and keep blood sugar levels high, factors associated with a greater likelihood of developing disease. As regards consumption of meat in particular, the rules developed at an international level by the World Cancer Research Fund (WCRF) apply: do not exceed the dose of 350–500 grams per week of red and white meat (the weight refers to cooked meat) and reduce preserved and canned meats and sausages to minimal quantities, or avoid them altogether. The same diet also applies in case of illness, but with a recommendation. Do-it-yourself is prohibited. High-protein diets, fasting, and too much physical activity stimulates inflammation processes or weakens the organism, favoring the vitality of oncogenic cells [65].

Research demonstrates that there is a connection between microbiota and cancer therapies. Intestinal microbiota metabolites influence the efficacy of chemotherapeutics and could be used in combined therapies. However, the molecular mechanisms underlying this encouraging evidence are not yet clear: future research must therefore also investigate in this direction. Moreover, microbiota can push the immune system to be more active against cancer cells, favoring a faster recovery on a physical and psychological level in case of cancer interventions and therapies. Some studies are demonstrating an unexpected action of a particular dietary regime, like the pharmacological one. It has been developed an innovative approach with very limited caloric restriction over time, which has the aim of affecting cancer cell metabolism and modifying that of the organism [66].

There is a lot of research, but there is still no certainty regarding the consumption of milk and dairy products. Some research shows that consumption of dairy products leads to a decrease in gastrointestinal cancer risk, with mixed results for cancers that depend on hormones, i.e., breast, prostate, endometrium and ovary, and for those that affect kidney, thyroid and lung [67]. It is also very important the so-called "chrono-nutrition", *i.e.*, choosing the optimal time of day for different foods.

Therefore, it can be concluded that Lactobacilli can influence the onset and prognosis of non-cervical gynecological cancer, but also positively influence the efficacy and tolerability of oncological therapies, which tend to negatively alter the Lactobacilli quota, and this much in therapies against uterine and breast cancer. The integration of *L. crispatus*, already tested for its high ability to orient the vaginotype towards CST-I state in HPV-positive women, will be useful both in cancer prevention and therapy, both of cervical and non-cervical ones [68, 69].

Microbiota integrates with:

- prebiotics: substances, especially fiber, present in food, which are not absorbed by the body but are used by the intestinal flora as a source of carbon to grow better. Prebiotics facilitate the growth of a healthy microbiota. The most common prebiotic foods include artichokes, rich in inulin, which our bacteria are fond of, asparagus, beans and oats, bananas, and walnuts, but also garlic and onion. To be taken with attention to the variety and overall caloric load;
- probiotics: bacterial strains which, taken in adequate quantities and with precise medical indications, can bring physical and psychological benefits to our body. The ideal is to take them on medical prescription, with attention to the variety of strains to maintain biodiversity. Also interesting are pharmaceutical probiotics, which have a different composition to better adapt to a microbiota that changes with age;
- synbiotics: contain both prebiotics and probiotics, to be used always on the advice of a physician who is an expert on the subject [70, 71]; and
- postbiotics: they are bioactive compounds produced dur-

ing the fermentation of food or substrates by probiotics, or they can be components of non-living microbial cells themselves. Unlike probiotics and prebiotics, postbiotics are non-living and include a wide range of substances.

The interest in postbiotics is due to two fundamental aspects: the first is their ability to cross the intestinal vascular barrier and therefore to systemically influence the organism through the blood, effectively mediating the remote action of intestinal microbiota in other areas of the body, and the second is that they constitute a more precise and powerful therapeutic tool. Instead of transplanting or modifying microbiota, as is done in some studies, we can act downstream, directly administering only the beneficial metabolic products, sometimes common to multiple bacterial strains which however also produce substances not of therapeutic interest [72].

3. Conclusions

The human body hosts a large community of microorganisms, viruses, bacteria and fungi, which constitute human microbiota. It is now clear that these are not mere spectators, but important players in the biology of our health, as well as various diseases. Scientific studies have revealed that intestinal microbiota composition plays a significant role in numerous aspects of health, including the risk of developing cancer and the response to oncological treatments. The involvement of intestinal microbiota in cancer development appears evident and this provides a new potential target for screening and prevention, but numerous points remain to be clarified regarding the causality or otherwise of the associations between specific bacteria and cancer types. Alterations in the balance of intestinal microbiota (dysbiosis) are then at the center of numerous studies, to examine a possible association with various pathological states. Dysbiosis could represent both a cause and a consequence of various pathologies, including cancer, due to the potential influence exerted by intestinal microbiota on human health through microbial metabolites, modulation of the host's immunity and metabolism.

Three recent studies clarify how knowledge about microbiota could translate into advances in the field of oncology. A chronic inflammatory state predisposes to the onset of certain types of cancers, including those of the intestine. To reduce risk, it could be useful to modify microbiota by acting on diet. What we eat, in fact, regulates the variety and relative abundance of the microorganisms that colonize the intestine and that influence the immune system. Results from a study demonstrate that a diet rich in fermented foods increases gut microbiota diversity and reduces molecular signs of inflammation in healthy adults. Those who eat foods such as yogurt, kefir and fermented vegetables or drink kombucha have a higher number of species of microorganisms in the gut and this is more evident for those who consume fermented products. They also have less activated baseline immune cells and lower blood levels of pro-inflammatory proteins. Fermented foods could be valuable in counteracting reduction in microbiota diversity and increase in inflammation widespread in industrialized society [73, 74].

Chronic inflammation, fueled by an imbalance in microbiota composition, may be a risk factor in the development of some forms of cancer. A compromised microbiota can induce alterations in the intestinal environment, creating a favorable terrain for cancer cells growth. Furthermore, microbiota plays a crucial role in immune system regulation, as it modulates inflammatory response and can influence effectiveness of oncological therapies, including chemotherapy and immunotherapy. These circumstances open new perspectives in prevention and management of oncological diseases. Understanding and manipulating microbiota could potentially improve the effectiveness of cancer treatments, reduce side effects and optimize therapeutic responses. Optimizing treatments does not only mean having effective therapies, but also limiting the unwanted effects of therapies. Intestinal microbiota is not just a digestive system but plays a multi-functional role that goes beyond gastrointestinal system health and directly affects the field of oncology medicine. Research in this area is contributing significantly to our understanding of oncological diseases, offering promising prospects for the future [75–77].

Advances in cancer research demonstrate that supplementation therapy with specific nutraceuticals enhances the effectiveness of anticancer treatments through epigenetic modulation and intestinal microbiota. Tertiary prevention, after all, with therapy control and correct intake of medications, requires management as carefully as possible of side effects that could limit its administration or adherence. For some years now, oncology research has paid particular attention to the microorganisms that populate the intestine, and which appear to have a leading role in cancer prevention and treatment [78]. Intestinal microbiota communicates closely and continuously with all our organs and systems and deserves to be studied and valorized in prevention and treatment strategies in every medical specialty. It is a powerful director of health and disease and an underappreciated modulator of abdominal, visceral, pelvic and systemic pain. It is worth considering it and renegotiating a more collaborative coexistence, through far-sighted health projects starting from changing lifestyles and healthy eating.

In conclusion, in the literature, microbiota dysbiosis is often associated with gastrointestinal cancer as it is part of a shared ecosystem, but studies also highlight a potential link between intestinal microbiota and cancer in other body areas. A recent study evaluated the causal effect of gut microbiota on several types of common cancers [79]. To date, it is believed that there are potential associations between gut microbiota profiles and oncological risk, although it is difficult to distinguish whether bacterial disruption occurs as a cause or consequence of cancer. A potential causal role of gut microbiota in cancer development would imply that early stool examination could be a feasible practice for cancer screening to recognize populations at higher risk. Furthermore, modulation of intestinal microbiota could become a potential option in prevention. The direct connection of intestinal microbiota to oncology suggests a potential to improve the efficacy of treatments, reduce side effects and optimize therapeutic responses. A balanced intestinal flora is essential for maintaining the body's homeostasis and for preventing cancer development. The relationship between microbiota and oncology represents an extraordinarily promising and continually growing field of research.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

FB—designed the research study. CC—performed the research; analyzed the data. CR—provided help and advice on writing the text. FB and CC—wrote the manuscript and contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Franco Borruto is serving as one of the Editorial Board members of this journal. We declare that Franco Borruto had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to EH.

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