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Review

Insights into the roles of microbiome in non-sterile cavities cancers

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Abstract

The human microbiome represents the entire genome assembly of microorganisms colonizing the human body and comprises more than three million genes that encode thousands of metabolites, which cover several functions essential for the host health condition. Anatomical sites colonized by microorganisms include the skin, gastrointestinal, respiratory, urogenital, and reproductive tract, establishing commensal, mutual, or pathogenic relationships with the organism. The human microbiota is considered a dense 'organ' with multiple roles in nutrition, gastrointestinal tract development, and innate immunity training. Depending on the genetic predisposition, type of diet, health status, and lifestyle, this 'organ' seems to have a specific, unique signature, maintained quasi-stable, establishing symbiotic relationships with the host organism. The disruption of the dynamic balance is established between the human body and its microbiota leads to dysbiosis, which in its turn, could be the origin of a comprehensive spectrum of diseases, ranging from inflammatory, infectious, and cardiovascular diseases to cancer. In this review, we will present several types of malignancies (e.g., head and neck cancers, esophageal, colorectal, cervical, lung, bladder, and skin cancers) and the appearance of the resistance to antitumor therapies. In this minireview we present some insights regarding the implication of human microbiota in non-sterile cavities cancers.

Keywords Human microbiome, eubiosis, imbalance, cancer

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Introduction

The human microbiota comprises the totality of microorganisms that colonize the body, interact with some components, and influence its physiology. The human body is colonized by at least 2000 known microorganisms, 100 being pathogenic [WANG & al [1]), hosting 10^{13}–10^{14} microbial cells (SAVAGE [2]; BACKHED & al [3]; GILL & al [4]; URSELL &al [5]; SENDER & al [6]), more than or being close to the number of human body cells (3×10^{13}). The entire genome assembly of microorganisms colonizing the human body is called the microbiome and comprises more than three million genes that encode thousands of metabolites, which cover several functions essential for the host health condition. By other estimates, the microbiome probably exceeds 150 times the total number of human genes, estimated at 23,000 (VALDES & al [7]). The totality of effectively transcribed microbial genes forms the microbial transcriptome, the translated microbial proteins the proteome, and the metabolites produced by the microbiota the metabolome.

Being maintained in a sterile environment, the human embryo and fetus do not interact with the maternal microbiota before birth; then, during the first three years of life, the young infant experiences a dynamic evolution of the microbial communities, and by the fourth year, the composition of human microbiota becomes stable and is maintained, within limits, throughout life (PALMER & al [8]; DEKABORUAH & al [9]). Anatomical sites colonized by microorganisms include the skin, gastrointestinal, respiratory, urogenital, and reproductive tract, establishing commensal, mutual, or pathogenic relationships with the organism (OGUNRINOLA & al [10]; DEKABORUAH & al [9]). Although numerous anatomical sites vary in providing the conditions for good colonization with microorganisms, the most hospitable being the gastrointestinal tract, where 0.1–1 trillion microbial cells can coexist (PALMER & al [8]). The human microbiota is considered a dense 'organ' with multiple roles in nutrition, gastrointestinal tract development, and innate immunity training. Depending on the genetic predisposition, type of diet, health status, and lifestyle, this 'organ' seems to have a specific, unique signature, which is maintained quasi-stable, establishing symbiotic relationships with the host organism (ZOETENDAL & al [11]; ECKBURG & al [12]; WANG & al [1]). The gastrointestinal microbiota influences physiological processes such as intestinal absorption, metabolism of carbohydrates, proteins, vitamins, and other nutrients, energy supply, pathogen defense function, and early development of the immune system in newborns (SHARON & al [13]). A dynamic balance is established between the human body and its microbiota, which allows them to coexist and have mutually beneficial effects. However, at the same time, its disruption leads to dysbiosis, which in its turn, could be the origin of a comprehensive spectrum of diseases, ranging from inflammatory, infectious, and cardiovascular diseases to cancer (OGUNRINOLA & al [10]).

Particularities of human microbiota

Depending on the anatomical site, health status, personal hygiene, hormonal status, local biology, local environment, lifestyle, and type of diet of human individuals, microbial communities have different phyla and genera composition (REDINBO & al [14]). The integumentary microbiota is composed of *Actinomycetota* (*Actinobacteria*), *Bacteroidetes*, *Cyanobacteria*, *Bacillota* (synonym *Firmicutes*), and *Proteobacteria* phyla, the oral microbiota of *Bacillota*, *Proteobacteria*, *Bacteroidetes*, *Actinomycetota* and *Fusobacteria*, the intestinal microbiota of *Actinomycetota*, *Bacteroidetes*, *Bacillota*, *Verrucomicrobia* and *Enterobacteria*, respiratory tract microbiota of *Actinomycetota*, *Bacillota*, *Proteobacteria* and *Bacteroidetes*, the vaginal microbiota, predominantly *Bacillota* phylum (HOU & al [15]), and the urinary microbiota, of *Bacillota*, *Actinomycetota*, *Fusobacteriota* and *Pseudomonadota* phyla (in women) (PEARCE & al [16]), and of *Bacillota* (predominantly), *Actinomycetota*, *Fusobacteriota*, *Proteobacteria*, and *Bacteroidetes* phyla (in men) (NELSON & al [17]).

Skin microbiota

Human skin is composed of the dermis (inner layer) and epidermis (outer layer), the latter comprising layers of differentiated keratinocytes, of which the outer layer (*stratum corneum*) consists of enucleated, differentiated, squamous, interconnected cells that contribute to the barrier function of intact skin. The skin provides different types of habitats for microbial communities: oily, sebum secreting microenvironments (on the face, chest and back), which are colonized by *Propionibacterium*, *Staphylococcus*, *Corynebacterium* and *Streptococcus* bacterial and *Malassezia*, *Aureoumbra*, *Tilletia*, *Pycnococcus*, *Gracilaria*, *Pyramimonas*, *Parachlorella* and *Leucocytozoon* fungal genera; moist microenvironments, with sweat secretion (armpit, elbow crease, popliteal space, groin space, spaces between toes), which are colonized by *Corynebacterium*, *Staphylococcus*, *Propionibacterium*, *Micrococcus* and *Enhydrobacter* bacterial and *Malassezia*, *Tilletia*, *Pyramimonas*, *Parachlorella*, *Aspergillus*, *Zymoseptoria*, *Nephroselmis*, *Trichophyton*, *Gracilaria* and *Cyanophora* fungal genera; and dry microenvironments (forearm and palm), which are colonized

by *Propionibacterium*, *Corynebacterium*, *Streptococcus*, *Micrococcus*, *Staphylococcus*, and *Veillonella* bacterial and *Malassezia restricta*, *Aspergillus*, *Candida parapsilosis*, *Zymoseptoria*, *Epidermophyton*, *Pyramimonas* and *Nannizzia* fungal genera; in all these niches some viruses can be also temporarily found, but do not penetrate the skin and do not cause infection. However, the presence of fungi can cause infections (e.g., oral or vaginal candidiasis) (BYRD & al [18]) (Figure 1).

Oral microbiota

The oral cavity is a complex structure that provides connectivity to the outside and a moist environment suitable for the development of a large number of microorganisms in a dynamic balance, the disruption of which leads to dysbiosis and the development of oral or systemic diseases. The *Corynebacterium*, *Rothia*, *Actinomyces*, *Prevotella*, *Capnocytophaga*, *Porphyromonas*, *Streptococcus*, *Granulicatella*,

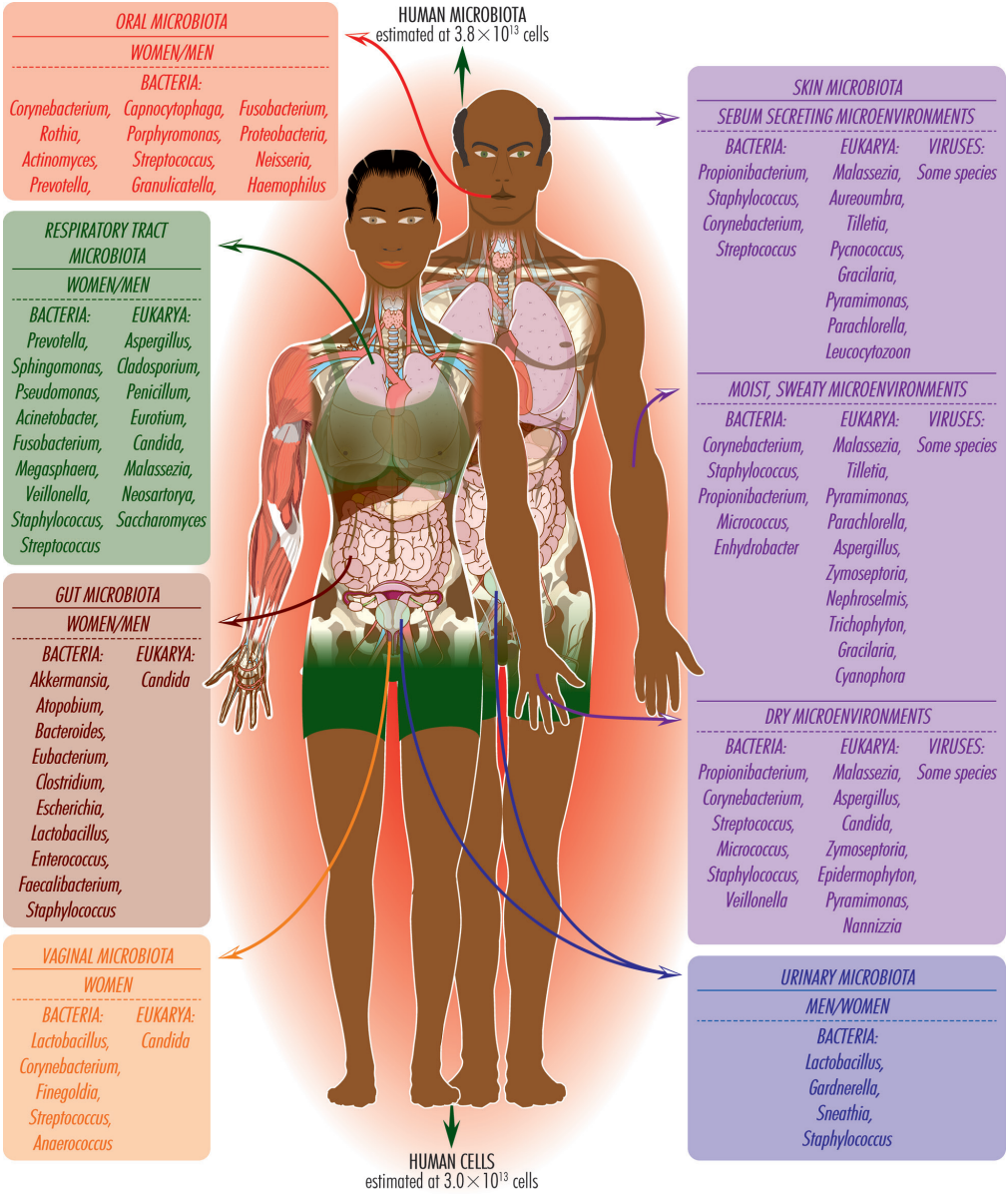

Fig.1. Main genera that colonize different anatomic niches of the human body.

Fusobacterium, *Proteobacteria*, *Neisseria*, and *Haemophilus* are among the genera most often found in the oral cavity of healthy individuals (LI & al [19]) (Figure 1).

Gut microbiota

The surface area of the human gastrointestinal tract is between 250 and 400 square meters, representing one of the most extensive interfaces between the human body's internal environment, microbiota, the immune system, and environmental factors, such as materials resulting from food digestion. During a human's lifetime, approximately 60 tons of material laden with numerous microorganisms pass through the gastrointestinal tract (THURSBY & JUGE [20]). These begin to colonize shortly after birth and include bacteria, archaea, and eukaryotic microorganisms, which establish relationships of commensalism and symbiosis in a balance that benefits both parties [BACKHED & al [3]). Of the more than 2000 species of commensal microorganisms, the majority (including at least 800 species of bacteria) (EL-SAYED & al [21]) are present in the gastrointestinal tract, where they form a real 'organ", integrated into the so-called 'superorganism' together with the human body [LI & al [19]). The commensal bacterial genera found in the gut microbiota are mainly from *Akkermansia*, *Atopobium*, *Bacteroides*, *Eubacterium*, *Clostridium*, *Escherichia*, *Lactobacillus*, *Enterococcus*, *Faecalibacterium*, and *Staphylococcus* (KHO & LAL [22]) genera, and among the fungi, *Candida albicans (*PEREZ [23]) (Figure 1). The bacterial concentration increases in the small intestine from the jejunum, where it is about 102–103 cells/gram, to the ileum, where it is about 107–108 cells/gram, to reach about 1011 cells/gram in the cecum and ascending colon and to carry out most of the metabolic reactions in the human gastrointestinal tract (NEISH [24]). In the transverse and distal colon, the concentration of microbiota decreases as it is eliminated with feces (Figure 2).

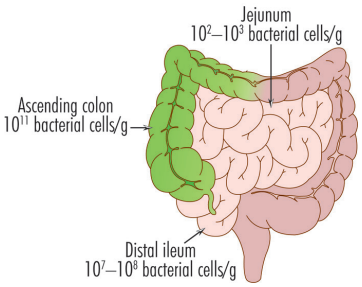

Figure 2. Increase in bacterial concentration in the intestines, from the jejunum, where the concentration is reduced, on average, to 10^2–10^3 bacteria/gram, to the ileum, where it reaches 10^7–10^8 cells/gram, and up to the cecum, ascending colon and proximal part of the transverse colon (illustrated in green), where the highest concentration of microorganisms is reached, on average 10^{11} bacteria/gram. This is where the main metabolic reactions occur, such as the fermentation of cellulose and the synthesis of short-chain fatty acids, with the microorganisms acting synergistically or antagonistically with anti-tumor therapies. From the proximal part of the transverse colon onwards, the number of bacteria/gram decreases, due to elimination with faces.

Respiratory tract microbiota

The respiratory tract is a complex anatomical entity that exchanges gases between the internal and external environment. The upper respiratory tract directs, heats, filters, and humidifies the inspired air, providing, in its compartments, varied environmental conditions for the bacterial genera *Prevotella*, *Sphingomonas*, *Pseudomonas*, *Acinetobacter*, *Fusobacterium*, *Megasphaera*, *Veillonella*, *Staphylococcus* and *Streptococcus*, and the fungal genera *Aspergillus*, *Cladosporium*, *Penicillium*, *Eurotium*, *Candida*, *Malassezia*, *Neosartorya* and *Saccharomyces* (Figure 1), which colonize them and prevent the growth of pathogenic microorganisms (SANTACROCE & al [25]).

Vaginal microbiota

The vagina is a cavitary organ, lined by the vaginal mucosa and providing specific conditions for the growth of bacteria of the *Lactobacillus*, *Corynebacterium*, *Finegoldia*, *Streptococcus,* and *Anaerococcus* genera (Figure 1), which limit the growth of pathogenic microorganisms, and *Candida* fungi, frequently associated with candidiasis (CHEE & al [26]).

Urinary microbiota

The microbiota of the human urinary tract is poorly investigated. The few studies conducted on it in healthy women categorize it into urotypes based on the relative abundance of the *Lactobacillus*, *Gardnerella*, *Sneathia*, and *Staphylococcus* genera, and individuals of the *Enterobacteriaceae* family (PEARCE & al [16]), with the genus *Lactobacillus* being involved in bladder health and frequently predominant, in women with urinary incontinence individuals of *Actinobaculum schaalii*, *Actinomyces neuii*, *Aerococcus urinae*, *Arthrobacter cumminsii*, *Corynebacterium coyleae*, *Gardnerella vaginalis*, *Oligella urethralis*, and *Streptococcus anginosus* are abundant, lactobacilli being rare (MARTINEZ & al [27]). The microbiota of the healthy male urinary tract is predominantly represented by *Bacillota*, *Actinomycetota*, *Fusobacteria*, *Proteobacteria*, and *Bacteroidetes*, with a very low abundance of *Tenericutes* and *TM7*, and is similar to that of the female urogenital tract or the integumentary or colonic microbiota (NELSON

& al [17]). The seminal microbiota of infertile men is enriched in *Aerococcus* and depleted in *Collinsella*; infertility appears to influence the rectal microbiota, which manifests decreased abundance in *Anaerococcus* and increased abundance in *Lachnospiraceae*, *Collinsella*, and *Coprococcus* in parallel with enrichment of the urinary microbiota in *Anaerococcus* (LUNDY & al [28]) (Figure 1).

Eubiosis *versus* dysbiosis

The colonizing of the body shortly after birth allows microorganisms to form simple communities, dominated by a few major bacterial groups, in different sites (predominantly in the gastrointestinal tract) and establish commensal and symbiotic relationships with it. As new species of microorganisms colonize the organism, simple communities evolve into a diverse (ROGIER & al [29]) and balanced ecosystem. Since ancient times, scientists have recognized the importance of a balance between gut microbiota components, dominated by beneficial species from the phyla *Bacillota* and *Bacteroides* (a state termed *eubiosis*). In contrast, potentially pathogenic species from the phyla *Proteobacteria* are present in a reduced proportion. In this regard, the most famous physician of ancient Greece, Hippocrates of Kos, stated over 2400 years ago that poor digestion is at the origin of all ills in the body, and death resides in the intestines (LICHTENSTEIN [30]). In the 19th century, the Russian zoologist and immunologist Ilya Ilyich Mechnikov recognized the importance of the microbiota in the gastrointestinal tract in maintaining health and triggering the disease. He said that most diseases stem from the inability of beneficial bacteria to control harmful ones, a condition he called *dysbiosis* (IEBBA & al [31]).

Eubiosis and human health

The eubiosis state is built through long-term cooperation between the host and the colonizing microbiota of the gastrointestinal tract. This is highly diverse and balanced; it includes a large number of microorganisms (KHO & LAL [22]; EL-SAYED & al [21]) and is involved in the metabolism of indigestible compounds in dietary fibers, such as cellulose, hemicellulose, pectin, xyloglucans, fructo-oligosaccharides, and oligosaccharides, making them available for intestinal absorption, providing about 10% of the body's energy and contributing to some extent to the maintenance of energy homeostasis (CHASSARD & al [32]; FLINT & al [33]). In addition, microorganisms in the gastrointestinal tract also release essential nutrients to the human body, including vitamins, can contribute to the detoxification of the body, occupy niches that opportunistic pathogenic microorganisms can colonize and affect their growth, enhance the activity of the immune system, and play an essential role in defining the intestinal architecture and maintaining the integrity of the colon (HOOPER & GORDON [34]; ROUND & MAZMANIAN [35]).

Cellulose is a polysaccharide present in plant cell walls. It consists of a linear chain of hundreds or thousands of (1→4)beta-glucose molecules linked to D-glucopyranose (CUMMINGS [36]) and fermenting microorganisms of the genera *Ruminococcus*, *Clostridium*, *Butyrivibrio*, and *Enterococcus*, as well as the species *Bacteroides cellulosilyticus*, present in the human gastrointestinal tract (CHASSARD & al [32]; FUJIMORI [37]), digest it to cellodextrin (WEIMER [38]), which can subsequently be hydrolyzed to glucose or to short-chain fatty acids, including acetic, propionic and butyric acids, hydrogen, carbon dioxide and methane (CUMMINGS [36]). With the help of microorganisms in the gastrointestinal tract, the digestibility of cellulose ingested from natural sources, such as fruits, vegetables, and cereals, is about 70-80% (PRYNNE & SOUTHGATE [39]). Pectin is a generic term for a series of polysaccharide polymers of galacturonic acid that enter the structure of plant cell walls and are digested almost entirely (CUMMINGS [40]) by the activity of microbiota in the human gastrointestinal tract by intervening in starch digestion and blood glucose regulation (by increasing the viscosity of colonic contents and inhibiting amylase activity), in the physical stimulation of the colon and the growth and balancing of the intestinal microbiota, while promoting, through fermentation, the production of short-chain fatty acids (BAI & GILBERT [41]). Xyloglucans are a group of branched polysaccharides ubiquitously present in the plant cell wall. They are metabolized by some microorganisms, such as the species *Bacteroides ovatus*, present in the gut microbiota (LARSBRINK & al [42]). Fructo-oligosaccharides and oligosaccharides, for which the human body has no intrinsic degradation mechanisms, are metabolized by species of the commensal and probiotic bacterial genera *Lactobacillus* and *Bifidobacterium* (GOH & KLAENHAMMER [43]). By metabolizing these compounds, microorganisms in the gastrointestinal tract produce 50-100 mmol·L–1 of short-chain fatty acids, which are rapidly absorbed through the colon wall, serving as precursors for the colonic mucosal lipids themselves or as a source of energy. They may also regulate intestinal motility, stimulating epithelial cell growth, inflammatory processes, and glucose homeostasis (WANG & al [1]; OGUNRINOLA & al [10]; FLINT & al [44]).

Gut microbiota (enterobacteria and species of the *Bifidobacterium* and *Bacteroides* genera) (OGUNRINOLA & al [10]) synthesize and supply the host with several essential

vitamins, including riboflavin (vitamin B2), biotin (vitamin B7/B8/H), folic acid and folate (vitamin B9), cobalamin (vitamin B12), vitamin K and other vitamins (WANG & al [1]). Riboflavin is involved in the breakdown of carbohydrates into glucose. Biotin is involved in the metabolism of carbohydrates, lipids, and proteins; folic acid and its salts play an essential role in cell regeneration, nucleic acid synthesis, and the production of red blood cells and leukocytes, cobalamin is synthesized from delta-aminolevulinate (KANG & al [45]) and serves as a cofactor for some biochemical reactions, and vitamin K is involved in the formation of proteins required for hemostasis, including prothrombin, by carboxylation of glutamic acid residues.

Food can become contaminated with toxic compounds and elements, including cadmium, mercury, chromium, lead, arsenic, etc., in small amounts but sufficient to create imbalances and induce various diseases (MONACHESE & al [46]). Metals introduced with food are sequestered by intestinal microorganisms to 40–60%, except for methylmercury, with a sequestration rate of about 10% (MONACHESE & al [46]). The divalent cadmium, Cd(II), a carcinogenic and toxic transition element, is retained in the gut by *Enterococcus faecium* resistant to this metal, which can also bioaccumulate divalent lead, Pb(II) (TOPCU & BULAT [47]; CHENG & al [48]. *Lactobacillus fermentum* and *Bifidobacterium longum* can reversibly bind these two metals (TEEMU & al [49]), and the *Lactobacillus plantarum* strain CCFM8610 has been shown to be protective against acute cadmium poisoning in mice (ZHAI & al [50]) or humans (ZHU & al [51]). Mercury is a transition metal with poorly soluble but highly toxic compounds that reach the intestine in the inorganic form, Hg(II), more soluble and with higher toxicity, or Hg2(II), less soluble and less toxic, or in the form of methylmercury, both forms affecting its microbiota. Several microorganisms resistant to mercury ions and present in the human gastrointestinal tract, *Sutterella parvirubra* and *Acidaminococcus intestini*, are involved in the degradation of mercury compounds (WATSON & al [52], especially monomethylmercury, which demethylates and reduces its toxicity (GUO & al [53]), especially in the presence of proteins. Hexavalent chromium, Cr(VI), in the form of chromate, CrO42–, and dichromate, Cr2O72– ions, which has the highest toxicity of all chromium ions, is bioaccumulated by living (23.8 mg Cr/g dry weight) and dead (39.9 mg Cr/g dry weight) cells of *Bacillus coagulans*, which can colonize the human gut only under artificial, controlled conditions, and produces lactic acid (SRINATH & al [54]). Arsenic is also a highly toxic and carcinogenic element, both in the trivalent form, As(III), interacting with the sulfhydryl (–S–H) groups present in polypeptide chains, which affect their functionality (MONROY-TORRES & al [55]), as well as in the pentavalent form, As(V), its ingestion altering the structure of the gut microbiota, favouring the development of arsenic-resistant bacterial genera, including *Bilophila*, *Desulfovibrio*, and *Bacillus* (BRABEC & al [56]), or arsenic-tolerant species, including *Escherichia coli* (WANG & al [57]). The gut microbiota plays a very important role in arsenic metabolism, influencing its oxidation states, degree of methylation, bioavailability, and excretion (CORYELL & al [58]). *Faecalibacterium prausnitzii*, a commensal species in the human gastrointestinal tract, may provide some protection against arsenic compounds (CORYELL & [59]). *Pediococcus acidilactici*, *Lactobacillus helveticus*, *and Streptococcus thermophilus* naturally present in the gut contribute to reducing the concentration of toxic organic molecules, such as polycyclic aromatic hydrocarbons, including benzopyrenes, and heterocyclic aromatic amines from fried, roasted or smoked meat products. *Lactobacillus sakei* and *Pediococcus pentosaceus* synthesize bacteriocins active against the opportunistic species *Pseudomonas aeruginosa* and *Escherichia coli* (STIDL & al [60]; BARTKIENE & al [61]).

Studies in animal models raised under sterile conditions that have never come into contact with microorganisms and studies manipulating the microbiota using selective antibiotics have provided evidence that the microbiota plays an essential role in immune homeostasis and autoimmunity (WU & WU [62]). Thus, antigen-presenting cells in Peyer's patches located in the intestinal wall synthesize higher levels of IL10 (interleukin 10) than antigen-presenting cells in the spleen (IWASAKI & KELSALL & al [63], and macrophages close to the gut microbiota develop a noninflammatory phenotype and do not produce proinflammatory cytokines when encountering microbial stimuli under homeostatic conditions (SMYTHIES & al [64]). Gut microbiota is involved in the regulation of neutrophil numbers (WU & WU [62]), IL22+NKp46+ NK cell differentiation (SANOS & al [65], and mast cell migration by expressing CXCR2 ligands on gut epithelial cells in a MyD88-dependent manner, an adaptor in the TLR signaling pathway (KUNII & al [66]). Commensal microorganisms in the gastrointestinal tract promote the residence of phagocytes, which concentrate bacterial antigens in gut-associated lymphoid tissue, activating T and B lymphocytes (YOO & al [67]). Naïve CD4+ T lymphocytes thus activated can be differentiated into four major subtypes, T helper 1 (Th1), Th2, Th17, and regulatory T cells (Treg), which produce different transcription factors and cytokines, and on CD8+ T lymphocytes, the gut microbiota plays a regulatory role, with the gut microbiota modulating the activity of plasmacytoid dendritic cells, invariant natural killer T cells, and marginal zone B lymphocytes. Present in Peyer's

patches in the intestinal wall, B lymphocytes mainly secrete immunoglobulin A (IgA) (WU & WU [62]).

Dysbiosis and human diseases

Imbalance of the gut microbiota, caused by various factors (e.g., antibiotic treatment, surgery, immunodeficiency associated with HIV1 infection), with the development of dysbiosis, underlies the development of many human diseases, including intestinal symptoms, infections, inflammatory diseases, allergies, liver disease, heart disease, metabolic disorders, psychiatric diseases and neoplasia (Table 1).

Frequently caused by antibiotic treatment, which kills or inhibits the growth of susceptible strains and favors the multiplication of resistant strains, including pathogenic ones, intestinal dysbiosis causes the appearance of clinical symptoms, including bloating (associated with *Anaerotruncus colihominis*, *Ruminococcus callidus*, *Lachnospira pectinoschiza*) (JALANKA-TUOVINEN & al [68]; BELIZARIO & FAINTUCH [69]), abdominal pain, associated with reduced abundance of bifidobacteria and diarrhea, correlated with increased abundance of *Anaerotruncus colihominis* and *Ruminococcus callidus* species (JALANKA-TUOVINEN & al [68]) and significant reduction of streptococci, especially *Streptococcus alactolyticus* species (HERMANN-BANK & al [70]; ZHANG & al [71]). Along with surgical interventions, the antibiotic treatment causes the multiplication of *Clostridioides difficile* (formerly designated *Clostridium difficile*) species (WEI & al [72]), whose toxins produce pseudomembranous colitis, and of *Escherichia coli*, *Enterococcus faecalis*, and *Enterococcus faecium*, which can cause septicemia, and *Bacteroides fragilis*, which induces intra-abdominal infections and abscesses (WILCOX [73]; ZHANG & al [71]). Periodontal disease, driven by the great multiplication of *Porphyromonas gingivalis*, *Prevotella intermedia*, *Fusobacterium nucleatum*, and *Treponema denticola* species, simultaneously with decreasing numbers of *Aggregatibacter actinomycetemcomitans* species, favors *Helicobacter pylori* infection (HU & al [74]). HIV1 infection is favored by vaginal inflammation produced by microorganisms such as *Prevotella bivia*. Colonization of the body with tenofovir-breaking microorganisms (e.g., *Gardnerella* sp.) leads to the failure of this otherwise highly effective treatment (COHEN [75]). The combination between the antiretroviral drug and a microbicidal gel leads to destroying bacteria. The microbicidal gel acts non-selectively on a broad spectrum of microorganisms, favoring uncontrolled multiplication of species from the *Bacillota* or *Bacteroidetes* phyla and disrupting, in the long term, intestinal eubiosis (COHEN [75]; LING & al [76]).

Inflammatory bowel diseases affect large numbers of people in developed regions of the world and can have several causes, including (1) interaction between commensal bacteria and the host; (2) aggressive Th1 lymphocyte-mediated cytokine response to the presence of gut microorganisms; (3) errors in recognition of commensal bacteria by macrophages; (4) defects occurring in some of the 163 loci involved in bacterial detection and clearance, which sensitize hosts and cause them to emit an exacerbated immune response to the commensal microbiota (HOENTJEN & al [77]; JOSTINS & al [78]). There are two types of idiopathic inflammatory bowel disease: (1) ulcerative colitis, localized to the colon, favored by the bacterial genera *Yersinia*, *Shigella*, *Salmonella*, *Campylobacter*, *Clostridium* and *Aeromonas*, associated with significantly reduced lactobacilli population and increased numbers of *Escherichia coli* and bacteria of the order *Clostridiales* in the active inflammatory phase, and with the presence of *Lactobacillus salivarius*, *Lactobacillus manihotivorans* and *Pediococcus acidilactici* species in the remission phase [CUMMINGS & al [79]), and (2) Crohn's disease, originally considered an autoimmune disease, but favored by a decrease of *Dialister invisus*, *Faecalibacterium prausnitzii*, *Bifidobacterium adolescentis* and *Clostridium* cluster XIVa species, and an increase of *Ruminococcus gnavus* (JOOSSENS & al [80]), or, in the pediatric form, by increasing abundance of *Enterobacteriaceae*, *Pasteurellacaea*, *Veillonellaceae* and *Fusobacteriaceae* families and decreasing abundance of *Erysipelotrichales*, *Bacteroidales* and *Clostridiales* orders representatives (GEVERS & al [81]).

The gut microbiota structure influences the development of cow's milk allergies; the abundance of *Clostridia* and *Bacillota* in the gut microbiota of 3–6-month-old infants is associated with the resolution of these allergies by the age of 8 years (BUNYAVANICH & al [82]).

The liver and the intestine interact closely, forming the gut-gut axis (GIANNELLI & al [83]). In this interaction, the liver releases the secreted compounds into the intestine, which is absorbed in the body and receives about 75% of its blood from the intestine *via* the portal vein, enriched in cellular and humoral immune components (MOROWITZ al [84]). On the other hand, through fermentation of food debris in the colon, the microbiota generates alcohol, ammonia, and acetaldehyde, which influence liver function and metabolism, and endotoxins, which influence Kupffer cell activity and cytokine production (NARDONE & ROCCO [85]). Dysbiosis of the small intestine, with impairment of the *Pseudomonadota*, *Actinomycetota*, *Bacteroidetes*, and *Bacillota* phyla and amplification of the phyla *Proteobacteria* (*Escherichia* species and other species of

the *Enterobacteriaceae* family), *Actinomycetota*, and *Bacteroidetes* (*Bacteroides* and *Prevotella* genera), the latter appearing decreased in some studies (MANZOOR & al [86]), and of the genera *Veillonella*, *Streptococcus* and *Clostridium* (CHEN & al [87]; QIN & al [88]), may contribute to the onset and progression of non-alcoholic liver disease (non-alcoholic steatohepatitis) (WU & al [89]); gut microbiota suppression after antibiotic treatment contributes to the onset of liver inflammation and Concanavalin A lectin-induced hepatitis (KAJIYA & al [90]), which can asymptomatically progress to liver cirrhosis. In cirrhotic individuals, the multiplication of pathogenic bacteria from the *Enterobacteriaceae*, *Veillonellaceae*, and *Streptococcaceae* families (CHEN & al [87]; ZHANG & al [91]; QIN & al [88]), which produce lipopolysaccharides leads to a relative decrease in indigenous commensal taxa, including *Lachnospiraceae*, *Ruminococcaceae*, and *Clostridia* (phylum *Bacillota*). Also, a decrease in *Bacteroidetes*, short-chain fatty acid-producing bacteria (BETRAPALLY & al [92]; CHEN & al [87]; BAJAJ & al [93]; MASLENNIKOV & al [94]) and of *Lachnospiraceae*, *Ruminococcaceae*, and *Blautia*, which hydroxylate primary bile acids and convert them to secondary bile acids (RIDLON & al [95]; KAKIYAMA & al [96]) has been observed in these individuals. Reduced bile acid concentration favors colonization of the small intestine with oral commensal bacteria of the species *Veillonella* sp. and *Streptococcus salivarius* (ZHANG & al [91]; CHEN & al [97]), which produce urease and break down urea into carbon dioxide and ammonia, likely contributing to endotoxemia in people with cirrhosis. The breakdown of urea due to dysbiosis and the inability of the liver to convert toxic ammonia to non-toxic urea due to cirrhosis lead to ammonia accumulating in the blood and crossing the blood-brain barrier, triggering the main complications of cirrhosis, cerebral edema, and hepatic encephalopathy (MANZOOR & al [86]).

Food-derived choline is converted to trimethylamine N-oxide in the liver, which is released into the intestine. Intestinal *Escherichia coli* converts trimethylamine N-oxide to trimethylamine, which is absorbed into the blood and can promote atheroma plaque formation and chronic heart failure (SANDEK & al [98]; DE GOTTARFI & MCCOY [99]). Intestinal dysbiosis, with reduction of *Faecalibacterium*, *Subdoligranulum*, *Roseburia*, *Eubacterium rectale*, and *Bacteroides fragilis* taxa, which regulate T-lymphocyte functions and secure an anti-inflammatory and protective response of the intestinal barrier, and colonization of the intestine with *Streptococcus*, *Escherichia*, *Shigella* and *Enterococcus* species, which adhere to the intestinal wall, disrupts intestinal microcirculation, increase intestinal permeability, favor the production of proinflammatory cytokines and amplify inflammation, with increased risk of chronic heart failure (MASENGA & al [100]). Further permeabilization of the intestinal barrier is favored by colonization with *Escherichia coli*, *Klebsiella pneumoniae*, and *Streptococcus viridians*. In contrast, the presence of *Lactobacillus brevis* has the opposite effect, inhibiting the activation of proinflammatory cytokines (ZHANG & al [91]). Colonization of the gut with *Lactobacillus plantarum* strains CECT 7527, 7528, and 7529, which assimilate cholesterol from the environment and produce bile salt hydrolysis, may help reduce cholesterol and coronary heart disease risk (BOSCH & al [101]). Increased cholesterol can trigger other cardiovascular diseases significantly when associated with hypertension. In hypertensive individuals, the gut microbiota is patchily distributed, its reduced abundance and diversity favoring the overgrowth of *Klebsiella*, *Desulfovibrio*, and *Prevotella* genera and decrease of *Blautia*, *Butyrivibrio*, *Clostridium*, *Enterococcus*, *Faecalibacterium*, *Oscillibacter*, *Roseburia*, *Bifidobacterium*, and *Lactobacillus* genera (WANG & al [102]).

With a branched-chain amino acid release, gut dysbiosis is involved in the pathogenesis of metabolic diseases, including obesity, insulin resistance, and type 2 diabetes. In obesity, the intestine is overpopulated with bacteria of the *Bacillota* phyla (e.g., *Dorea formicigenerans*, *Dorea longicatena*, *Lactobacillus reuteri*, *Staphylococcus aureus*, and some species of the class *Mollicutes* (TURNBAUGH & al [103]; COMPANYS & al [104]; HU & al [105]; GENG & al [106]) and *Actinomycetota* (*Collinsella aerofaciens*) [TURNBAUGH & al [107]; COMPANYS & al [104]), which occupy the niches vacated by *Akkermansia*, *Faecalibacterium*, *Oscillibacter*, and *Alistipe* (THINGHOLM & al [108]). Translocation of some species (*Proteus mirabilis* and *Escherichia coli*) from the gut to specific tissues induces inflammation, which affects the serum metabolome and induces insulin resistance and its progression to type 2 diabetes, *via Prevotella copri* and *Bacteroides vulgates* (MARTINEZ-LOPEZ & al [109]).

The close link between the gut and the brain has been recognized for many decades and is called the gut-brain axis. Since the gut microbiota is essential for normal brain function and involves the nervous, endocrine, immune, and metabolic systems, the concept of the gut-brain axis is extended to that of the microbiota-gut-brain axis (CRYAN & DINAN [110]). The microbial translocation into the intestinal wall and mesenteric lymphatic tissue trigger a complex immune response, releasing proinflammatory cytokines and the involvement of the vagus nerve and afferent spinal nerves. Autism spectrum disorders appear to be associated with relative decreases in the mucolytic bacteria *Akkermansia muciniphi-*

Table 1. Summary of pathological conditions in which quantitative alterations of human microbiota (dysbiosis) have been reported

Type of condition	Microorganisms with exacerbated multiplication	References	Microorganisms with decreased multiplication	References
bloating	*Anaerotruncus colihominis*, *Ruminococcus callidus*, *Lachnospira pectinoschiza*	(JALANKA-TUOVINEN & al [68]; BELIZARIO & FAINTUCH [69])		
diarrhea (incl. post antibiotic treatment)	*Anaerotruncus colihominis*, *Ruminococcus callidus, Clostridioides difficile*, *Escherichia coli*, *Enterococcus faecalis*, *Enterococcus faecium*, *Bacteroides fragilis*	(JALANKA-TUOVINEN & al [68]; WEI & al [72]; WILCOX [73]; ZHANG & al [71]).	*Streptococcus alactolyticus*	(HERMANN-BANK & al [70])
periodontal disease	*Porphyromonas gingivalis*, *Prevotella intermedia*, *Fusobacterium nucleatum*, *Treponema denticola*	[HU & al [74])	*Aggregatibacter actinomycetemcomitans*	[HU & al [74])
ulcerative colitis	*Yersinia*, *Shigella*, *Salmonella*, *Campylobacter*, *Clostridium*, *Aeromonas*	CUMMINGS [36])	Lactobacilli	(CUMMINGS [36])
Crohn's disease (adult)	*Dialister invisus*, *Faecalibacterium prausnitzii*, *Bifidobacterium adolescentis*, *Clostridium* cluster XIVa	(JOOSSENS & al [80])	*Ruminococcus gnavus*	(JOOSSENS & al [80])
Crohn's disease (pediatric)	*Enterobacteriaceae*, *Pasteurellacaea*, *Veillonellaceae*, *Fusobacteriaceae*	(GEVERS & al [81]).	*Erysipelotrichales*, *Bacteroidales*, *Clostridiales*	(GEVERS & al [81])
non-alcoholic liver disease	*Proteobacteria (Enterobacteriaceae), Actinomycetota*, *Bacteroidetes* (*Bacteroides, Prevotella*), *Veillonella*, *Streptococcus*, *Clostrisdium*	(CHEN & al [87]; QIN & al [88])	*Pseudomonadota*, *Actinomycetota*, *Bacteroidetes*, *Bacillota*	CHEN & al [87]; QIN & al [88]), MANZOOR & al [86])
cirrhosis	*Enterobacteriaceae*, *Veillonellaceae*, *Streptococcaceae, Akkermansia muciniphila*	(CHEN & al [87]; QIN & al [88]); ZHANG & al [91])	*Lachnospiraceae*, *Ruminococcaceae*, *Clostridia* (relative), *Bacteroidetes*, *Blautia*	(CHEN & al [87]; BAJAJ & al [93]; MASLENNIKOV & al [94]); (RIDLON & al [95]; KAKIYAMA & al [96])
reduced bile acid concentration	*Veillonella* sp., *Streptococcus salivarius*	(CHEN & al [87]; ZHANG & al [91])		
inflammation and increased risk of chronic heart failure	*Lactobacillus*, *Streptococcus*, *Escherichia*, *Shigella, Enterococcus*	MASENGA & al [100])	*Faecalibacterium*, *Subdoligranulum*, *Roseburia*, *Eubacterium rectale, Bacteroides fragilis*	MASENGA & al [100])
permeabilization of the intestinal barrier	*Escherichia coli*, *Klebsiella pneumoniae*, *Streptococcus viridians*	(ZHANG & al [91])		
hypertension	*Klebsiella*, *Desulfovibrio*, *Prevotella*	WANG & al [102]).	*Blautia*, *Butyrivibrio*, *Clostridium*, *Enterococcus*, *Faecalibacterium*, *Oscillibacter*, *Roseburia*, *Bifidobacterium*, and *Lactobacillus*	WANG & al [102]).
obesity	*Bacillota* (*Dorea formicigenerans*, *Dorea longicatena*, *Lactobacillus reuteri*, *Staphylococcus aureus*, *Mollicutes*), *Actinomycetota* (*Collinsella aerofaciens*)	TURNBAUGH & al [103]; COMPANYS & al [104]; BACKHED & al [3]; HU & al [105]; GENG & al [106])	*Akkermansia*, *Faecalibacterium*, *Oscillibacter*, *Alistipe*	(THINGHOLM & al [108])
type 2 diabetes	*Prevotella copri*, *Bacteroides vulgates*	(MARTINEZ & al [27])		
autism			*Akkermansia muciniphila, Bifidobacterium* spp.	(WANG & al [111])
schizophrenia	*Lactobacillus fermentum*, *Alkaliphilus oremlandii*, *Cronobacter sakazakii/turicensis*, *Enterococcus faecium*; significant multiplication of *Succinivibrio*, *Megasphaera*, *Collinsella*, *Clostridium* (*Clostridium coccoides*), *Clostridioides difficile*, *Klebsiella*, *Methanobrevibacter*	(MUNAWAR & al [112])	*Coprococcus*, *Roseburia*, *Blautia*, *Bifidobacterium*, *Lactobacillus*, *Escherichia coli*	(MUNAWAR & al [112])

la and *Bifidobacterium* spp. (WANG & al [111]), schizophrenia, with an abundance of facultatively anaerobic bacteria, including *Lactobacillus fermentum*, *Alkaliphilus oremlandii*, *Cronobacter sakazakii/turicensis*, *Enterococcus faecium*, with significant multiplication of *Succinivibrio*, *Megasphaera*, *Collinsella*, *Clostridium*, *Klebsiella* and *Methanobrevibacter* genera, and *Clostridium coccoides* and *Clostridioides difficile* species. Meanwhile, there was a reduction of *Coprococcus*, *Roseburia*, *Blautia*, *Bifidobacterium* and *Lactobacillus* genera, and *Escherichia coli*. *Clostridioides difficile* produces and releases phenylalanine derivatives, which control catecholamine levels; in schizophrenia, catecholamines, especially dopamine, have elevated levels (MUNAWAR & al [112]).

Nonsterile anatomic sites and cancer

The cancer etiology is multifactorial, including (1) genetic causes (hereditary factors related to inherited genetic predispositions, including specific mutations, weakening of loci, deletions, activation of proto-oncogenes and inactivation of tumor suppressor genes), (2) external factors, including the introduction of carcinogens or procarcinogens; (3) internal factors, related to the metabolism of procarcinogens into carcinogens, alteration of the local microenvironment and stress conditions, with the production of reactive oxygen species and attenuated or abnormal functioning of the immune system; and (4) microbial factors, especially when microbiota becomes altered (dysbiosis) and enriched in microorganisms producing compounds with a genotoxic effect..

The human microbiota is associated with several malignancies that often occur at sites colonized by microorganisms (e.g., skin, head and neck, digestive and genitourinary tract). Thus, human papillomaviruses (HPV) are involved in oral, oropharyngeal, and cervical neoplasia etiology. In addition, Helicobacter *pylori* causes gastric and probably esophageal cancer and altered gut microbiota structures are associated with colorectal cancer. Thus, adenoma and colorectal cancer are characterized by an abundance of potentially pathogenic bacteria from the genera *Pseudomonas*, *Helicobacter*, and *Acinetobacter* and decreased butyric acid-producing bacteria. In addition, the periodontal pathogen *Fusobacterium nucleatum* and the species *Bacteroides massiliensis*, *Bacteroides ovatus*, *Bacteroides vulgatus*, and *Escherichia coli* are present in high numbers during the progression from adenoma to colorectal cancer, promoting inflammation and influencing the tumor microenvironment (WANG & al [1]).

Head and neck cancers

Head and neck cancers occur in the upper aerodigestive tract (nasal cavity, oral cavity, pharynx, and larynx), more than 90% originating in squamous cells lining the mucosa (CONSTANTIN [113]) and are the sixth most common cancer worldwide (ARGIRIS & al [114]). In 2020, the number of new cases of head and neck cancers was estimated to be over 900,000 [International Statistical Classification of Diseases and Related Health Problems [115]) or 931,931, of which 699,840 new cases were in men and 232,091 new cases were in women (FERLAY & al [116]; SUNG & al [117]). Among the risk factors for head and neck cancers are: heavy smoking (active and passive) and alcohol consumption, which contribute to about 72% of cases, chewing betel quid (Areca nuts), poor oral hygiene with the colonization of the oral cavity by pathogenic microorganisms, consumption of fried, smoked or roasted meat, which introduces carcinogens and procarcinogens into the body, inhalation of chemical compounds and asbestos dust, genetic factors (TRIZNA & SCHANTZ [118]; FOULKES & al [119]; ARGIRIS & al [114]), and HPV (human papillomavirus) and EBV (Epstein-Barr virus) infections, involved in the etiology of about 25% of cases (MEHANNA & al [120]; CONSTANTIN [113]). Head and neck cancers rarely metastasize, in about 10% of cases, but are highly locally invasive, strongly affecting the physiology and functionality of the active region. Therefore, when diagnosed at early stages, they can be successfully treated by including cytoreductive surgery and/or radiotherapy/local chemotherapy treatment, with a complete cure and no long-term impairment of functionality. Most head and neck cancers are diagnosed at advanced stages when they invade and involve several anatomical structures, including locoregional lymph nodes, with impaired functionality of the area and reduced treatment options. In these cases, standard therapeutic approaches include cytoreductive surgery, radiotherapy and chemotherapy, and sometimes innovative therapies such as photodynamic therapy, immune checkpoint inhibitor therapy, oncolytic virus therapy, use of therapeutic vaccines, chimeric antigen receptor T-cell therapy, targeted therapies to treat head and neck cancers (targeting EGFR/ERBB1 (epidermal growth factor receptor), VEGF (vascular endothelial growth factor), VEGFR (vascular endothelial growth factor receptor), MET (mesenchymal-epithelial transition factor), RET, CDK4/6, FGFR, RAS, RAF, MEK, ERK, PI3K-AKT-mTOR, JAK-STAT, NOTCH, aurora kinases, cellular inhibitors of apoptosis and epigenetic modifications) and therapies using antibody-drug conjugates. Despite so many therapeutic approaches, head and neck cancers have a very high risk of recurrence,

high mortality of around 50% at five years after diagnosis (especially for primary laryngopharyngeal/hypopharyngeal tumors) and, although cured, if risk factors (e.g., smoking, alcohol consumption and consumption of Areca nuts in the form of betel quid) are present, they maintain a high lifetime risk of death. In the prognosis of head and neck cancers, oral and oropharyngeal microbiota play an important role, with *Fusobacterium nucleatum* being present at early stages and associated with good prognosis and prolonged survival (CHEN & al [121]), *Veillonella* being associated with favorable prognosis,and *Stenophotromonas*, *Staphylococcus*, *Centipeda*, *Selenomonas*, *Alloscordovia* and *Acinetobacter* being associated with poor prognosis and reduced survival (GRANATO & al [122]). HPV infection, on the other hand, generally confers a favorable prognosis and reasonable response to treatment (FELDMAN & al [123]).

Esophageal cancers

Esophageal cancers affect the upper digestive tract between the hypopharynx/laryngopharynx and the stomach, including two significant subtypes, i.e., esophageal squamous cell carcinoma, which occurs predominantly in the proximal portion of the esophagus, and esophageal adenocarcinoma, which usually occurs in the distal esophagus (YANG & al [124]). Esophageal squamous cell carcinoma originates in the lining of the esophageal squamous cell epithelium and is prevalent (more than 90% of cases) in China, Japan, and southeastern African countries (LIN & al [125]; HE & al [126]) and southern Europe [HUANG & YU [127]), and esophageal adenocarcinoma originates from glandular cells near the stomach, is more closely related to gastroesophageal junctional carcinomas or gastric cancer, and is predominant in the United States, Australia, and Western Europe (VIZCAINO & al [128]; CASTRO & al [129]; ISLAMI & al [130]). Worldwide, esophageal cancers are the eighth or ninth (if all head and neck cancers, including in the sixth position, are added together) most common cancer type, with 604,100 new cases in 2020, including 418,350 new cases in men and 185,750 new cases in women (FERLAY & al [116]; SUNG & al [117]; MORGAN & al [131]). Esophageal cancers are aggressive and have a low five-year survival rate of only 10-30%, with 24% in Australia and 36% in Japan (MORGAN & al [131]), ranking sixth in mortality (YANG & al [132]). The main risk factors for esophageal adenocarcinoma are Caucasian race, male gender, gastroesophageal reflux disease, smoking (active or passive, current or history of smoking), and obesity (HUANG & YU [127]), with neoplasia advancing in the order gastroesophageal reflux disease – Barrett's esophagus – esophageal adenocarcinoma (SHORT & al [133]; WANG & al [1]), and for esophageal squamous cell carcinoma, smoking, alcohol consumption, and achalasia (SHORT & al [133]). In both cases, esophageal microbiota may be a predisposing factor, with *Lactobacillus* overgrowth being detected in esophageal adenocarcinoma and contributing to acidification of the esophageal environment. In contrast, esophageal *Helicobacter pylori* is considered a risk factor for esophageal squamous cell carcinoma [ZHOU & al [134]). Although esophageal cancer cases have improved only slightly recently, innovative treatments may offer some favorable outcomes ((YANG & al [132]).

Gastric cancer

Gastric cancer affects the lining of the stomach and ranks fifth most common cancer worldwide, with 1,089,103 new cases in 2020, including 719,523 new cases in men and 369,580 new cases in women (FERLAY & al [116]; SUNG & al [117]), and fourth in cancer-related deaths. Thus, in 2020, 768,793 deaths in people with gastric cancers were estimated, of which 502,788 in men and 266,005 in women (FERLAY & al [116]). More than 95% of gastric cancers are adenocarcinomas, diffuse, infiltrating the gastric wall in the desmoplastic stroma and associated with hereditary genetic abnormalities, or intestinal, with the formation of mass lesions and predominantly associated with *Helicobacter pylori* infection (AJANI & al [135]). In addition to genetic factors and bacterial infection, gastric cancer is also favored by smoking, alcohol consumption, high salt intake, salted, smoked and processed meat and fish, spicy food consumption, HPV infection, sedentary lifestyle, vitamin C deficiencies (YUSEFI & al [136]). Since gastric cancer is diagnosed in advanced stages, the prognosis is guarded, with a low five-year survival rate in European and North American countries of 10-30%, but relatively good in Japan of 90%, where endoscopic digestive tract monitoring programs are implemented (SITARZ & [137]).

Colorectal cancer

Colorectal cancer affects the distal digestive tract and is the third most common type and the second most deadly worldwide. In 2020, there were an estimated 1,931,590 new cases, of which 600,896 in men and 547,619 in women, and 576,858 deaths (FERLAY & al [116]; SUNG & al [117]), and statistics indicate an increasing trend in both variables, particularly in the elderly (HOSSAIN & [138]). Risk factors for the occurrence of colorectal cancer include age (77% of people diagnosed with colorectal cancer are between 50 and 77 years of age (STEELE & [139]), family history of familial adenomatous polyposis and Lynch syndrome (hereditary nonpolyposis colorectal cancer), obesity, physical inactivity, regular alcohol consumption, active or passive

smoking, red or processed meat, colon dysbiosis with a multiplication of bacteria from the genera *Pseudomonas*, *Helicobacter*, *Streptococcus*, *Bacteroides* and *Acinetobacter*, and hormonal changes associated with advancing age [WANG & al [1]; KEUM & GIOVANNUCCI & al [140]; HOSSAIN & [138]). Colon cancer occurs in both sexes in similar proportions, metastasizes less, is easier to treat, does not require a permanent colostomy, and is prone to complete cures more easily than rectal cancer. The latter is more common in men, metastasizes intensely, predisposes to colostomy, is challenging to treat, and offers little chance of cure (KRASTEVA & GEORGIEVA [141]). Because nearly 25% of colorectal cancers are diagnosed in an advanced stage, and cytoreductive surgery alone leaves room for the development of metachronous metastases in about 20% of cases, the current primary treatment consists of tumor resection and systemic chemotherapy, along with pre- or post-prep radiotherapy, to stabilize the tumor. However, in metastatic tumors, this combination offers poor prognosis and low survival rates [MESSERSMITH [142]; KEUM & GIOVANNUCCI & al [140]). As with other cancers, cell clones resistant to chemotherapeutic agents or radiation action become selected from colorectal tumors, producing recurrences and/or metastases, necessitating the introduction of new adjuvant therapies in their therapeutic strategies. Among the usable therapeutic modalities are immunotherapy, therapies targeting VEGF/VEGFR, EGF/EGFR, HGF (hepatocyte growth factor), MET, IGF/IGF1R (insulin-like growth factor/insulin-like growth factor 1 receptor), TGF (transforming growth factor), and Wnt/beta-catenin, Notch and hedgehog signaling pathways (XIE & al [143], but also nanoparticles (KRASTEVA & GEORGIEVA [141]).

Cervical cancer

Among cancers of the female genital tract, cervical cancer is the most common. Cervical cancers can originate in the exocervix's squamous epithelium or the endocervix's glandular epithelium. However, most of them occur between the two types of epithelia in the transformation zone (AMIN & al [144]. Cervical cancer affects many women, especially in countries where prevention of HPV infection, one of the main risk factors for this time of cancer, is not in place. Globally, cervical cancer ranks seventh or eighth (in statistics that include head and neck cancers as sixth) among the most common cancers, with 604,127 new cases and 341,831 deaths in 2020 (FERLAY & al [116]; SUNG & al [117]). Risk factors for cervical cancer include HPV16 and HPV18 infections (COHEN & al [145]), HIV infections (ADLER & al [146]), sexual promiscuity, a high number of sexual partners (REMSCHMIDT & al [147]), early start of sexual life, early pregnancy (LOUIE & al [148]) and oral contraceptive pills (ASTHANA & al [149]; ZHANG & al [150]).

Lung cancers

Worldwide, lung cancers rank second in terms of the number of cases, totaling approximately 2,206,771 new cases in 2020 (1,435,943 men and 770,828 women), and first in terms of the number of deaths, with 1,796,144 deaths (FERLAY & al [116]; SUNG & al [117]). Depending on the cells in which they originate, lung cancers are categorized into small-cell and non-small-cell cancers, the latter divided into several subtypes. According to the 2015 WHO classification, the most common are adenocarcinomas, followed by squamous cell cancers and neuroendocrine tumors, including small cell carcinoma, large cell neuroendocrine carcinoma, and carcinoid (TRAVIS & al [151]). Risk factors for lung cancer include tobacco smoking (active or passive), marijuana smoking, asbestos exposure, radon exposure (dense gas resulting from the radioactive decay of uranium), air pollution with polycyclic aromatic hydrocarbons, arsenic exposure, inflammation and respiratory tract infections including tuberculosis, chronic obstructive pulmonary disease, family history of lung cancer, which increases by 1. 7 times the risk of lung neoplasia (for first-degree relatives of lung cancer patients, the risk is 2-4 times higher, even in non-smokers), older age (around 70 years and older), gender (men are twice as exposed as women) (THANDRA & al [152]). The mortality of people with lung cancers is very high (LEMJABBAR-ALAOUI & al [153]).

Bladder cancers

Bladder cancers are the most common type of cancer of the urinary system, of which urothelial carcinoma has the highest prevalence (DOBRUCK & OSZCZUDLOWSKI [154]). Approximately 75% of newly diagnosed cases have tumors that do not invade muscle tissue, with the remainder being invasive neoplasms (PENG & al [155]). Worldwide, bladder cancer ranks 11th in number of cases, with 573,278 new cases (440,864 cases in men and 132,414 cases in women) and 212,536 new deaths in 2020 (FERLAY & al [116]; SUNG & al [117]), and its development is favored by age over 55, gender (men are more likely to develop bladder neoplasia), tobacco smoking, which causes about 30-40% of urothelial carcinoma cases and up to two-thirds of all bladder cancer cases, genetic predisposition, infections (gonorrhea – *Neisseria gonorrhoeae*, , other bacterial infections and parasitosis, such as schistosomiasis – *Schistosoma haematobium*) (Figure 5), and occupational exposure to various compounds, such as 4-aminobiphenyl, 2-naphthylamine and benzidine, which accounts for 5-10% of cases (HALASEH & al [156]).

Skin cancers

Skin cancers, including melanomas and non-melanomas, including basal cell carcinoma and squamous cell carcinoma, affect the integument and are caused primarily by unprotected exposure to ultraviolet radiation. Worldwide, melanomas accounted 324,635 cases (173,844 cases in men and 150,791 cases in women) in 2020, with 57,043 deaths, and non-melanomas of the skin ranked fifth with 1,198,073 cases, of which 722,348 in men and 475,725 in women and 63,731 deaths (FERLAY & al [116]; SUNG & al [117]). Skin cancers have a multifactorial etiology, the most important risk factor being exposure to natural or artificial ultraviolet radiation during tanning sessions. Thus, for melanomas occurring on exposed portions of the skin, these appear to be the main risk factor, while for those occurring on skin not exposed to the action of UV radiation, stimulation and physical pressure of the palms and feet. For basal cell carcinoma, the most common form of skin cancer in humans, ultraviolet B radiation with wavelengths of 290-320 nm is the main risk factor, and for squamous cell carcinoma, ultraviolet radiation and long-term use of immunomodulatory drugs (OH [157]). In addition to ultraviolet radiation, the etiology of skin cancers may involve the microbiota colonizing the integument (WOO & al [158]).

Resistance to antitumor therapies

The mechanisms by which antitumor drugs manifest their therapeutic potential include inducing damage to genetic material, binding to DNA and blocking its transcription and replication, inhibiting topoisomerases, inducing antitumor immune responses, blocking receptors and ligands involved in initiating the transmission of biological signals, etc. Usually, tumor cells activate mechanisms to overcome these effects, and the resulting clones proliferate, invade neighboring tissues, and metastasize. Resistance to antitumor therapies is a significant issue, which can lead to treatment failure and further tumor progression and this phenomenon can be influence by human microbiota composition. Among the mechanisms involved in acquiring treatment resistance in tumor cells are drug efflux (which is also a main menchanism of multidrug resistance in pathogens), evasion of apoptosis (also used as a pathogenic feature by intracellular pathogens), epigenetic changes (that can be also influenced by the metabolic activity of human microbiota), DNA damage repair (trigereed by the activation of the SOS response, also active in bacteria), and altered gene expression (SEVCIKOVA & al [159]). Drug efflux is commonly encountered and occurs *via* ABC (ATP-binding cassette transporters), also present in bacteria. These represent a 48-member family, of which only ABCB1, ABCC1, and ABCG are actively involved in the transport of chemotherapeutic agents (TOWNSEND & TEW [160]). For example, ABCB1, expressed in colorectal, liver, and lung tumor cells, clears daunorubicin, doxorubicin, paclitaxel, vinblastine, and vincristine (BOGMAN & al [161]), ABCC1 is involved in anthracycline efflux, camptothecin-epipodophyllotoxins, methotrexate, mitoxantrone, and vinca alkaloids (YIN & ZHANG [162]), ABCG2 is involved in the elimination of anthracyclines and mitoxantrones from breast tumor cells (KOMATANI & al [163]). Chemotherapy- and radiotherapy-induced breaks in genetic material can be repaired by homologous recombination, mismatch repair, non-homologous splicing of ends, and nucleotide excision repair (encountered in the repair of breaks produced by platinum-based agents (REARDON & al [164]), some leading to accumulation of mutations. Thus, lesions induced by platinum-based therapeutic agents are repaired by overexpression and enhancement of ERCC1 (DNA excision repair protein) and XPF (DNA repair Endonuclease) activity (ROSELL & al [165]. Epigenetic and histone modifications, which package DNA, play an essential role in developing resistance to antitumor therapy, including altered gene expression, DNA repair, anticancer drug efflux, and the bypass of apoptosis (WANG & al [166]). They are silenced by hypermethylation of tumor suppressor gene promoters (e.g., TP53, silenced in many tumor types but not in HPV-infected tumors). By hypomethylation of oncogene promoters and MDR1 (Demethylated promoter of multidrug resistance gene 1), they are reactivated, promoting tumor progression (KANTHARIDIS & al [167]; JIN & al [168]; HOUSMAN & al [169]). Changes in the tumor microenvironment may also contribute to the acquisition of chemotherapy resistance. Thus, cancer-associated fibroblasts shape the extracellular matrix, limiting the contact of chemotherapeutic agents with tumor cells (FU & al [170]) and activation of mesenchymal stem cells, which can become tumor cells, can overcome the effects of drugs by reducing caspase three activity (VIANELLO & al [171]; TENG & al [172]). In addition to these factors, gut or intratumoral dysbiosis may have a protective role for tumor cells, conferring resistance against chemotherapy.

Capecitabine (N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine) is an orally delivered prodrug, which, in the body, is converted to the cytotoxic 5-fluorouracil form *via* thymidine phosphorylase, predominantly active in liver and tumor cells (HUANG & al [173]). Further, uridine phosphorylase converts 5-fluorouracil to 5'-fluorouridine and then to 5-fluorouridine monophosphate (YAN & al [174]), a compound highly toxic to *Caenorhabditis elegans*. In this way, uridine phosphorylase reduces antitumor efficacy. Furthermore, it

induces the toxic effects of fluoropyrimidines (ROSENER & al [175]), while its abrogation reduces the systemic toxicity of 5-fluorouracil (CAO & al [176]). On the other hand, uridine phosphorylase converts, by phosphorolysis, the prodrug 5'-fluorouridine into 5-fluorouracil, the antitumor active form (WAN & al [177]).

Human microbiota has been shown to influence the activity of cyclophosphamide, capecitabine, oxaliplantin doxorubicin, 5-Fluorouracil, memcitabine and even immunotherapy. In some cases, the effect is synergic (e.g., due to microbial enzymes such as nitroreductase activity, stimulation of ROS release from myeloid cells by normal microbiota with the increase of the antitumoral immunity - TNF production), while in other cases microbiota acts antagonistically (e.g., increasing resistance through increasing autophagy, drug inactivation or degradation less active derivatives, upregulation of apoptosis) (CHIFIRIUC & al, 2022 [178]).

Conclusions

The dynamic balance established between the human body and its microbiota allows them to coexist and have mutually beneficial effects, while its disruption leads to dysbiosis. Imbalance of the gut microbiota, caused by various factors (e.g., antibiotic treatment, surgery, immunodeficiency associated with HIV1 infection), with the development of dysbiosis, underlies the development of many human diseases, including intestinal symptoms, infections, inflammatory diseases, allergies, liver disease, heart disease, metabolic disorders, psychiatric diseases, and neoplasia.

Investigating causal and molecular interactions between commensal microbes in mucosal body sites is expected to shed new light on human variability in cancer development, progression, and treatment responsiveness. The main challenges faced in such research are related to sample allocation, processing, sequencing, and data analysis, in addition to the need to evolve from a correlative to a causative understanding of microbial influences on cancer. Consequently, microbial contributions to cancer biology will likely take the first place in the next decade of cancer research while increasing cancer diagnosis, patient stratification, and treatment.

Author contributions

M.C., C.B., G.M. conceived and corrected the manuscript. O.C.V., S.T., M.M.M., R.E.C., I.C. contributed to the literature survey and revised the manuscript. M.C. and O.C.V. drafted the manuscript. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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