Review

The important role of breast microbiota in breast cancer

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# Equal contribution

Abstract: One in eight women will be diagnosed with breast cancer (BC) in their lifetime, resulting in over 2 million cases annually. BC is the most common cancer among women. Unfortunately, the etiology of majority of cases remains unknown. Recently, evidence has shown that the human microbiota plays an important role in health and disease. Intriguingly, studies have revealed the presence of microorganisms in human breast tissue, which was previously presumed to be sterile. Next-generation sequencing technologies have paved way for the investigation of breast microbiota, uncovering bacterial signatures that are associated with BC. Some of the bacterial species were found to possess pro-carcinogenic and/or anti-carcinogenic properties, suggesting that the breast microbiota has potentially crucial roles in maintenance of breast health. In this review, we summarize the recent findings on breast tissue microbiota and its interplay with BC. Bacterial signatures identified via next-generation sequencing as well as their impact on breast carcinogenesis and cancer therapies are reviewed. Correlation of breast tissue microbiota and other factors, such as geographical and racial differences, in BC is discussed. Additionally, we discuss the future directions of research on breast microbiota as well as its potential role in prevention, diagnosis and treatment of BC.

Keywords: breast cancer; microbiota; bacteria; dysbiosis; pro-carcinogenic; anti-carcinogenic; genetics; next-generation sequencing; cancer treatments; cancer prevention

1. Introduction

Breast cancer (BC) is the most common cancer among women and the second most frequent cancer overall with over 2 million cases globally each year [1]. In fact, one in eight women will be diagnosed with BC in their lifetime. Despite the substantial progress in treatment and diagnosis, BC is still the leading cause of cancer death among women worldwide [2]. Due to the complexity of cancer which involves a multitude of genomic and physiological changes, the precise etiology of majority of BC is still unknown. Moreover, only a portion of those with genetic predisposition to BC and those exposed to known environmental risk factors developed the disease [3]. At least 70% of BC cases happen in women with average risk and existing prediction models offer poor risk discrimination [4,5]. This suggests the urgent need to identify other contributing factors. Indeed, one such factor that has garnered attention recently is the human microbiota which consists of trillions of bacteria, viruses, archaea and eukaryotes of more than 10,000 different species that colonize human tissue at numerous body sites and contributes to human development [6]. Perturbation of the

dynamic microbial communities, termed dysbiosis, has been increasingly shown to correlate with many disorders including acute and chronic diseases ranging from obesity [7] to autism spectrum disorders [8,9] as well as BC [10,11].

Dysbiosis has also been linked to other types of cancer such as gastric adenocarcinoma caused by the well-studied *Helicobacter pylori* [12] and colorectal cancer associated with the emerging role of certain microbiomic profiles, including *Fusobacterium* [13,14]. It is becoming progressively evident that both discrete bacterial species and community composition can exert either pathogenic effects that lead to diseases or probiotic effects which maintain the health. In fact, infection with one or more microorganisms or viruses is the third largest cause of cancer, resulting in at least 20% of cases [15,16]. In relation to this, the human microbiota formed by the huge amount and diversity of microorganisms and viruses may have an underestimated association with cancer due to unrecognized mechanisms or infections [15]. Furthermore, mounting evidence indicates that microbial shifts are associated with cancer development and aggressiveness [17] whereas restoring the normal microbiota or removing the causative organism can reverse this process [18,19]. Hence, knowledge on the microbial signatures associated with specific cancers can offer insights into etiology, prevention, diagnosis and treatment.

The distinct nature of microbiota in each body niche indicates an organ specificity to microbial effects on carcinogenesis. It was previously believed that the breast tissue was sterile. However, microbiome analyses of breast tissue and milk have shown that the human breast harbors diverse and unique microbiota [11,20,21], which is at least partly originated from microorganisms reaching the ducts from the skin via nipple-oral contact through lactation and/or sexual contact as well as translocation of the gut microorganisms [22,23]. In this regard, it has been suggested that the breast microbiota supports the maintenance of healthy breast tissue by processes such as stimulating resident immune cells and degrading carcinogens through their metabolic activity [11]. Intriguingly, recent studies have correlated breast microbiota with BC and demonstrated pro-carcinogenic and/or anti-carcinogenic properties of certain bacterial species, suggesting a potentially important role of the microbiota in the disease development [23,24]. Furthermore, microbiota has also been found to affect the efficacy and toxicity of cancer treatments, signifying a novel strategy to exploit the microbiota to improve efficacy and reduce toxicity of the therapies. Albeit the study of breast microbiota is still in its infancy, these findings have provided an insight on the impact of breast microbiota on BC and highlighted the rationale for further exploring its role in the disease. In this review, we summarize the recent findings on breast tissue microbiota and its interplay with BC (Figure 1). Bacterial signatures of BC patients and healthy individuals identified via next-generation sequencing as well as their potential roles in breast carcinogenesis and cancer therapies are reviewed. Correlation of breast tissue microbiota and other factors, such as geographical and racial differences, in BC is also discussed. In addition, we discuss the future directions of investigations on breast microbiota as well as its impact on the prevention, diagnosis and treatment of BC.
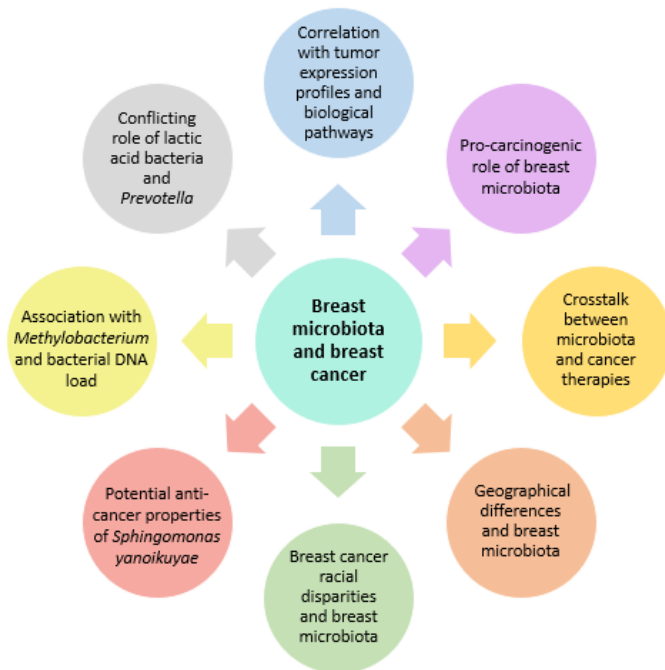
Figure 1. Interplay between breast microbiota and breast cancer.

2. Breast microbiota and breast cancer

Dysbiosis denotes the abnormal composition in microbial community of an organism, which can occur when proportions of certain species alter within the community. It hampers the symbiotic relationships in microbial community and disrupts the usual function of the community. Even though the largest microbial community of human resides in the gastrointestinal tract, it is necessary to consider the role of breast microbiota in BC due to the association between dysbiosis and the disease [10,11]. Hieken *et al*. [23] showed that the breast tissue had a microbiome which was different from that of the overlying breast skin and with a greater species richness. This indicates that though the breast tissue microbiome might be originated from the skin microbiome, breast tissue has a distinct ecosystem and environment. These differences may be caused by variances in tissue microenvironments, for instance oxygen levels and pH, which facilitate the relative dominance of specific taxa. In addition, the breast tissue microenvironment may be associated with the breast health which allows the growth of certain bacterial species that are otherwise unable to grow in a different health condition.

Notably, unique microbial signatures including bacterial, viral, fungal and parasitic signatures present in breast tumor tissues have been associated with the four major types of BC, namely endocrine receptor (ER) (estrogen or progesterone receptor) positive, human epidermal growth factor receptor 2 (HER2) positive, triple positive (estrogen, progesterone and HER2 receptors positive) and triple negative (estrogen, progesterone and HER2 receptors negative) BCs [25,26]. Moreover, the alteration in breast microbiota correlates with the histological grade [27] (Table 1) of

the disease. These alterations affect functional changes, such as the up-regulation of glycerophospholipid and ribosome biogenesis as well as the down-regulation of flavonoid biosynthesis, as the grade of BC increases [27]. Hence, these suggest the potential use of microbial and pathway signatures as biomarkers for diagnosis and staging of BC. Recently, the role of breast tissue microbiota in BC has been investigated. The results of clinical studies on BC and human breast microbiota in which the bacterial 16S rRNA gene was sequenced are summarized in Table 1, highlighting the predominant bacteria found in breast tissue as well as the differentially abundant bacteria identified in healthy individuals and patients with BC or benign tumor. Most of the investigations have demonstrated a predominance of the phyla *Proteobacteria* and *Firmicutes* in breast tissue [11,21,24,25] (Table 1). Nevertheless, the functionality of breast microbiota may ultimately have a more essential role in BC than its composition. Studies have shown the ability of microbiota to regulate chronic inflammation and immunity, genomic stability and DNA damage as well as metabolic function of the host which may modulate the risk of BC. These roles and the possible mechanisms of specific breast microbiota that impacts BC development are further discussed in the following sections of this review.

Table 1. Human studies on breast microbiota in relation to breast cancer.

Study	Sampling materials and sample size	Microbiota detection and OTU picking method	Predominant bacteria in breast tissue	Differentially abundant bacteria in BC, benign or control
Xuan *et al.*, 2014 [11]	Breast tumor tissue and paired normal adjacent breast tissue from 20 ER+ BC patients	Pyrosequencing gDNA amplified 16S V4 rDNA, QIIME: Greengenes database	*Proteobacteria* *Firmicutes* *Actinobacteria* *Bacteroidetes* *Verrucomicrobia*	Breast tumor tissues: *Methylobacterium radiotolerans* ──── Normal adjacent breast tissues of BC: *Sphingomonas yanoikuyae*
Urbaniak *et al.*, 2014 [21]	Breast tumor tissue and normal breast tissue from 81 women: 43 Canadian (27 BC, 11 benign, 5 healthy) and 38 Irish (33 BC, 5 healthy)	Ion Torrent V6 16S rRNA sequencing, QIIME: Ribosomal Database Project SeqMatch tool	*Proteobacteria* *Firmicutes* *Actinobacteria* *Bacteroidetes* *Verrucomicrobia* *Fusobacteria* *Deinococcus-Thermus*	Breast tumor tissues: *Escherichia coli*
Urbaniak *et al.*, 2016 [24]	Normal adjacent breast tissue: 58 patients (45 BC, 13 benign) Normal breast tissue: 23 healthy women	16S V6 rRNA amplicon sequencing, QIIME: SILVA database	*Proteobacteria* *Firmicutes*	Normal adjacent breast tissues of BC: *Bacillus* *Staphylococcus* *Enterobacteriaceae* (unclassified) *Bacteroidetes* (unclassified) *Comamondaceae* (unclassified) ──── Normal breast tissues: *Lactococcus* *Streptococcus* *Prevotella* *Corynebacterium*

Micrococcus

Table 1. Cont.

Study	Sampling materials and sample size	Microbiota detection and OTU picking method	Predominant bacteria in breast tissue	Differentially abundant bacteria in BC, benign or control
Hieken *et al.,* **2016 [23]**	Normal adjacent breast tissue: 13 benign and 15 invasive BC (all ER+ and PR+, 29% HER2+)	16S V3-V5 rDNA hypervariable taq sequencing, IM-TORNADO: Greengenes database	*Proteobacteria* *Firmicutes* *Actinobacteria* *Bacteroidetes*	Normal adjacent breast tissues of BC: *Fusobacterium* *Lactobacillus* *Atopobium* *Hydrogenophaga* *Gluconacetobacter*
Wang *et al.,* **2017 [10]**	Breast tumor tissue and paired normal adjacent breast tissue: 57 BC patients Normal breast tissue: 21 healthy women	Illumina 16S V3-V4 rRNA amplification, QIIME: Greengenes database	Not specified	Breast tumor tissues: *Alcaligenaceae* Normal breast tissues: *Methylobacterium*
Thompson *et al.,* **2017 [28]**	668 breast tumor tissues (HER2+, ER+, TNBC) and 72 normal adjacent tissues from TCGA Breast tissues from 6 ER+ patients submitted to TCGA	16S V3-V5 rRNA gene sequencing, IM-TORNADO: Greengenes database	*Proteobacteria* *Firmicutes* *Actinobacteria*	Breast tumor tissues: *Proteobacteria* *Mycobacterium fortuitum* *Mycobacterium phlei* Normal adjacent breast tissues of BC: *Actinobacteria* *Escherichia coli* *Haemophilus influenzae*

Table 1. Cont.

Study	Sampling materials and sample size	Microbiota detection and OTU picking method	Predominant bacteria in breast tissue	Differentially abundant bacteria in BC, benign or control
Meng *et al.*, 2018 [27]	Breast tumor tissue: 72 BC, 22 benign	16S V1-V2 rRNA gene amplicon sequencing, QIIME: Greengenes database	*Proteobacteria* *Firmicutes* *Actinobacteria* *Bacteroidetes*	Malignant breast tumor tissues: *Proteobacteria* *Propionicimonas* *Micrococcaceae* *Caulobacteraceae* *Rhodobacteraceae* *Nocardioidaceae* *Methylobacteriaceae*
				Malignant breast tumor tissues with lower histological grade: *Bacteroidaceae*
				Malignant breast tumor tissues with higher histological grade: *Agrococcus*
Costantini *et al.*, 2018 [29]	Breast tumor tissue and paired normal adjacent breast tissue: 16 BC patients	16S V2, V3, V4, V6+7, V8, and V9 rRNA gene amplicon sequencing, Ion Reporter Software: MicroSEQ(R) 16S Reference Library and Greengenes database	*Proteobacteria* *Firmicutes* *Actinobacteria* *Bacteroidetes*	Breast tumor tissues: *Methylobacterium* *Ralstonia*
				Normal adjacent breast tissues of BC: *Sphingomonas* *Methylobacterium*

Table 1. Cont.

Study	Sampling materials and sample size	Microbiota detection and OTU picking method	Predominant bacteria in breast tissue	Differentially abundant bacteria in BC, benign or control
Smith *et al.*, 2019 [30]	Breast tumor tissue and paired normal adjacent breast tissue: 64 BC patients Normal breast tissue: 8 healthy women	16S V4 rRNA gene sequencing, QIIME: Greengenes database	*Proteobacteria* *Firmicutes* *Bacteroidetes* *Actinobacteria*	Breast tumor tissues: *Pseudomonadaceae* *Clostridia* *Bacteroidia* *WPS_2* *Ruminococcaceae* *Fusobacteria* *Spirochetes* *Xanthomonadaceae* (Non-Hispanic White) *Ralstonia* (Non-Hispanic Black) Normal adjacent breast tissues of BC: *Pseudomonadaceae* *Sphingomonadaceae* *Caulobacteraceae* Normal breast tissues: *Actinomycetaceae*

BC: breast cancer; ER+: estrogen receptor positive; PR+: progesterone receptor positive; HER2+: human epidermal growth factor receptor 2 positive; TNBC: triple negative breast cancer; TCGA: The Cancer Genome Atlas; OTU: operational taxonomic unit; QIIME: Quantitative Insights Into Microbial Ecology; IM-TORNADO: Illinois Mayo Taxon Organization from RNA Dataset Operations.

3. Breast microbiota is correlated with tumor expression profiles and biological pathways

Thompson *et al.* [28] utilized BC data from The Cancer Genome Atlas (TCGA) to characterize breast microbiota and investigate the correlation between these OTUs and host tumor expression profiles. Geneset enrichment indicated that the tumor gene expression was associated with *Listeria fleischmannii* and to a smaller extent, with *Neisseria subflava*. *L. fleischmannii* was found to be more strongly correlated with expression profiles of genes involving epithelial-to-mesenchymal transition, which is implicated in tumor progression with metastatic expansion and the development of tumor cells with stem cell properties that are essential in resistance to cancer therapies [31-33]. On the other hand, *Haemophilus influenzae* was associated with genes representing pathways essential to tumor growth, which are E2F transcription factors, G2M checkpoint and mitotic spindle assembly [28]. *H. influenzae* is an opportunistic pathogen that has been shown to induce inflammatory immune response and enhance tumor growth in lung cancer murine models [34,35]. The increased presence of this bacterium in non-cancerous adjacent samples indicated that it may primarily reside in the neighboring stromal tissue. Indeed, the oxidative tumor environment might prohibit *H. influenzae* penetrance as the bacterium has been shown to be susceptible to H_2O_2. Taken together, these findings have shed light onto the possible mechanisms in which breast microbiota affects BC development, whereby certain bacterial species exhibit their pro-carcinogenic roles by modulating the host gene expression.

Meanwhile, Hieken *et al.* [23] examined the functional roles of the breast microbiota using KEGG pathways for analysis and found 6 differentially abundant pathways between malignant and benign disease states. The pathways involving methionine and cysteine metabolism, C5-branched dibasic acid metabolism, fatty acid biosynthesis and glycosyltransferases were depleted in patients with malignant disease. Intriguingly, methionine dependence is a common metabolic defect in many cancers and it has been proposed that cancer progression can be reversed by depleting methionine with a methionine-restricted diet or methioninase [36,37]. Thus, the results indicated that the breast microbiota may also be involved in breast carcinogenesis by modulating the biological pathways of the host. The secretion of bacterial metabolites which enter the circulation to reach their target cells is a main pathway in microbiome-to-host signaling [38,39]. In regard to this, the role of bacterial metabolites is similar to the human hormones that are synthesized in a gland or an organ and transferred to other anatomical sites, where they exert their biological effects. These blood-borne microbial metabolites such as short-chain fatty acids [40,41], lithocholic acid [42-44], deconjugated estrogens [45,46] and cadaverine [47] were shown to regulate the behavior of BC. Such bacterial metabolites have profound effect on mitochondrial metabolism. Notably, metabolites also modulate other metabolic processes, for instance lipid metabolism [48].

4. Pro-carcinogenic role of breast microbiota

A study was performed by Urbaniak *et al.* [24] to determine whether the breast tissue microbiome could play a role in regulating the risk of BC development. Bacterial signatures were found to be statistically different between the normal adjacent tissue in BC women and control tissue. Higher relative abundances of *Enterobacteriaceae*, *Bacillus*, *Staphylococcus*, *Bacteroidetes* and *Comamondaceae* were found in BC patients, while *Lactococcus*, *Streptococcus*, *Prevotella*, *Corynebacterium* and *Micrococcus* were the most abundant in healthy controls [24]. *Escherichia coli* strains, which belong

to the family *Enterobacteriaceae*, are known to harbor *pks* pathogenicity island that encodes the machinery to produce the genotoxin colibactin. The ability of these *pks*-positive strains to induce chromosomal instability and DNA double-stranded breaks [49,50] through colibactin has been linked to colon cancer [51,52]. Hence, this led Urbaniak *et al.* [24] to isolate the bacteria from normal adjacent tissue of BC patients and evaluate for their abilities to cause DNA damage via histone-2AX (H2AX) phosphorylation (γ-H2AX) assay. The isolated *E. coli* and *Staphylococcus epidermidis* induced DNA double-stranded breaks in HeLa cells [24], which may explain their higher abundances in cancer patients. Moreover, Thompson *et al.* [28] have also reported that *E. coli* was more abundant in breast tissues and was shown in higher abundance within non-cancerous adjacent breast tissues. Similarly, in a previous study by Urbaniak *et al.* [21], a greater abundance of the cancer-promoting *E. coli* was also observed in breast tissues from cancer patients compared to healthy controls.

Women who are genetically susceptible to BC or have mutations in DNA checkpoint or DNA repair machinery may be more prone to bacterially induced DNA damage. Thus, they might be at a greater risk of developing BC than women without these mutations, even when the same harmful microbes are present in their mammary glands [24]. These findings suggest that both the presence of mutations in DNA checkpoint or DNA repair machinery and the presence of pro-carcinogenic bacteria with DNA damaging properties within the breast microbiota may be a useful indicator of BC risk. Furthermore, *Micrococcus*, which was relatively abundant in healthy controls, as well as *Propionibacterium*, which had no difference in relative abundances between healthy controls and cancer patients, did not produce the DNA double-stranded breaks [24]. Therefore, these results further substantiated the association between BC and bacteria with DNA damaging properties that are highly abundant within the breast microbiota. On the other hand, although *Bacillus* did not inflict the DNA double-stranded breaks, *Bacillus cereus* cultured in the study by Urbaniak *et al.* [24] may possess other pro-carcinogenic effects and promote tumor development by metabolizing progesterone [53,54].

In Hieken *et al.*'s [23] study, the breast tissue microbiome was differentially abundant with the phyla *Proteobacteria*, *Firmicutes*, *Actinobacteria* and *Bacteroidetes* in descending order, similar with the findings from Urbaniak *et al.* [21]. The authors also demonstrated that the microbial communities were notably distinct between the normal breast tissue adjacent to invasive cancer and that adjacent to benign disease. Malignancy has been found to be associated with enrichment of taxa with lower prevalence such as the genera *Fusobacterium*, *Lactobacillus*, *Atopobium*, *Hydrogenophaga* and *Gluconacetobacter*. In fact, *Fusobacterium* has been linked to other epithelial malignancies, including colorectal cancer, by releasing virulence factors and producing a pro-inflammatory environment that progresses carcinogenesis [14,55-57]. Although the authors attributed menopausal status and age of patients as possible confounders of the observed differences, these results indicated the potential use of the microbial signatures as biomarkers for BC diagnosis.

5. Crosstalk between microbiota and cancer therapies

Dysbiosis can profoundly impact both cancer pathogenesis and its therapeutic outcome. Particularly, the regulation of therapeutic outcomes is closely associated with the ability of gut microbiota to metabolize anti-tumoral compounds and to modulate host's immune response as well as inflammation pathways [58]. As a result, this may explain the strong involvement of microbiota composition in affecting the effectiveness of both chemotherapy and immunotherapy [59]. Mounting

evidence suggests that gut microbiota affects the chemotherapy efficacy and toxicity by regulating the metabolism, translocation and immune response to the drugs [60]. Thus, it is likely that the local microbiota of the breast may have a distinct role in modulating chemotherapeutic effectiveness in addition to the known role of gut microbiota in regulating the efficacy of chemotherapeutics. This would indicate that the breast microbiota may play a critical role in the development of personalized cancer treatment, which can be targeted to enhance efficacy and reduce toxicity of existing chemotherapy agents. Hence, a greater insight into the impact of the microbiota on chemotherapeutic drugs is highly required. Moreover, the gut microbiota composition has also been found to modulate the toxic side effects caused by immunotherapy. It has been observed that toxic side effects in patients treated with anti-CTLA4 antibody are regulated by an increased abundance of *Firmicutes*, for instance *Faecalisbacterium*, as well as a decreased abundance of *Bacterioides* [61,62]. Furthermore, the microbiota has also been shown to correlate with the severity of radiotherapy-induced mucositis [63,64] and protect against radiation-induced toxicity [65]. This suggests the potential use of microbiota-based strategies in early prediction and prevention of radiotherapy-related complications. On the other hand, cancer therapies could also modulate the microbiota. Poly(ADP-ribose) polymerase (PARP) inhibitors, which are drugs that are potentially used as BC treatment [66,67] in future, were found to increase the diversity of gut microbiota [68,69]. Therefore, cancer treatments may impact the microbiota positively or negatively, which in turn affect the health of the host. Hence, the effects of cancer therapies on microbiota may have to be further examined.

Additionally, altering microbiota may deeply affect the outcome of anti-cancer therapies. Antibiotics were found to disrupt the microbiota resulting in a decreased response to platinum-based chemotherapies and immunotherapies [70]. This indicates that an intact microbiota is essential for optimal responses to cancer treatments. It has been revealed how tumor-bearing mice, either germ-free or with depleted gut microbiota through antibiotics therapy, have no response to oxaliplatin drug treatment. The elucidation is that commensal microbiome members in the gut of the mice may produce TLR agonists, hence promoting an oxidative stress milieu and causing tumor cell death. Consequently, there is a reduced microbiota-dependent ROS production without a healthy gut microbiota, which results in a less effective chemotherapeutic response [70]. Consistently, mice with lung tumors treated with cisplatin in combination with antibiotics, survive less and form bigger tumors. When cisplatin is combined with probiotics, for instance *Lactobacilli*, mice exhibit an improved response to the therapy. The mechanism involves the stimulation of pro-apoptotic genes within tumor mass and the augmentation of host's immune response [71]. Furthermore, the administration of a particular bacteria, *Alistipes shahii*, into antibiotic-treated tumor bearing mice, significantly improves the outcome of immunotherapy with restoration of tumor necrosis factor (TNF) production [70]. Probiotics and fecal microbiome transplantation are currently explored as anti-cancer adjuvants to combat dysbiosis following cancer therapies, to enhance chemotherapy and immunotherapy efficacy as well as to both decrease tumor mass and prevent tumor recurrence. Multiple translational studies further substantiate the crucial role of the gut microbiome in regulating the response to immune checkpoint blockade [72-74]. In particular, Routy *et al*. [72] showed that melanoma patients had a lower survival rate when treated with antibiotics in combination with anti-PD1/anti-PD-L1 immunotherapy.

Interestingly, correlative studies have also shown that antibiotic consumption, which reduces the microbiota diversity, increases the risk and recurrence of BC [75-79]. Despite the non-mechanistic nature of these investigations and the possibility for uncontrolled confounding, these studies support

the observations that the decrease in microbiota diversity increases the risk for BC. Taken together, the microbiota composition of cancer patients and the antibiotic regimens they receive during cancer treatments may have to be well considered. Additionally, the antibiotic consumption history of cancer patients may aid in the prediction of response to cancer therapies. Nonetheless, the effect of antibiotic regimens on the microbiota diversity and therapeutic outcomes in patients receiving cancer treatments needs to be further investigated. On the other hand, since mounting evidence has suggested that microbial dysbiosis is associated with BC, antibiotics may be useful to eradicate the causative organism or restore the normal microbiota to reverse the process. It is therefore essential to identify the factors which are able to affect the microbiota and develop novel strategies to manipulate it, with the main goal of improving the therapeutic outcome. Besides improving the efficacy of cancer therapies, interventions on microbiota may also be crucial to ameliorate cancer therapy-related toxicity [80,81].

6. Geographical differences affect the breast microbiota

In another study by Urbaniak *et al*. [21], the authors investigated the breast tissue microbiota of 81 women with and without cancer from two distant countries, Canada and Ireland to ensure that the findings were not the artifact of a single demographic. Consistent with other studies [11,24,25], *Proteobacteria* and *Firmicutes* were the most prevalent phyla among the diverse population of bacteria identified in tissue obtained from sites all around the breast, unlike their lower abundance in other body sites. The authors suggested that these findings may be a result of possible host microbial adaptation in the fatty acid environment of breast tissue, forming its unique microbiota that is distinct from that present at other body sites. The main OTUs identified were from 7 different phyla, *Proteobacteria*, *Firmicutes*, *Actinobacteria*, *Bacteroidetes*, *Verrucomicrobia*, *Fusobacteria* and *Deinococcus-Thermus*, where *Proteobacteria* was the most prevalent, followed by *Firmicutes* (particularly from the class *Bacilli*). Notably, the geographical difference between the Canadian and Irish women in the study appears to play a role in shaping the breast tissue microbiomes. The most prevalent taxa in Canadian samples were *Bacillus* (11.4%), *Acinetobacter* (10.0%), *Enterobacteriaceae* (8.3%), *Pseudomonas* (6.5%), *Staphylococcus* (6.5%), *Propionibacterium* (5.8%), *Comamonadaceae* (5.7%), *Gammaproteobacteria* (5.0%) and *Prevotella* (5.0%). Meanwhile, unclassified *Enterobacteriaceae* (30.8%), *Staphylococcus* (12.7%), *Listeria welshimeri* (12.1%), *Propionibacterium* (10.1%) and *Pseudomonas* (5.3%) were most abundant in the Irish samples [21]. Additionally, culture analysis confirmed the presence of viable bacteria in some of the samples. Although direct comparisons among the two countries are unable to be made because of the different collection and DNA extraction methods applied, further investigations may unveil the effect of geographical differences and perhaps cultural differences on breast microbiota and BC.

7. Breast cancer racial disparities and breast microbiota

Smith *et al*. [30] explored the normal and BC tissue microbiota from non-Hispanic White (NHW) and non-Hispanic Black (NHB) women to characterize distinct microbial signatures in race, stage or tumor subtype. It is well established that NHB women are more prone to be diagnosed with triple negative breast cancer and have the highest risk of BC death compared to all other ethnic groups [82-84]. The study was the first to reveal differences in breast tissue microbiota between the

races whereby a higher abundance of genus *Ralstonia* in breast tumors of NHB women in comparison to NHW tumors, which may explain part of the BC racial disparities. Notably, Costantini *et al.* [29] have found an increase of *Ralstonia* genus in cancerous samples relative to healthy-adjacent tissues from the same patient. Concomitantly, the authors have also reported decreased relative abundance of *Methylobacterium* in the cancerous samples, which is consistent with the findings of Wang *et al.* [10]. Costantini *et al.* [29] were the first to reveal that the genus *Ralstonia*, *Proteobacteria* phylum, is the most abundant genus in breast tissue since previously the genus had only been associated with human milk [85]. The findings of the increased relative abundance of *Ralstonia* in cancerous samples compared to healthy controls suggest possible pro-carcinogenic properties of the genus. Indeed, *Ralstonia* has been found to be correlated with most cancer types, including BC [86] and gastric cancer [87]. Therefore, it is plausible that the abundance of *Ralstonia* could be a biomarker of carcinogenesis. Furthermore, the interplay between racial differences and breast tissue microbiota in BC may suggest possible impact of genetics on the predisposition of the disease through its influence on the microbiota. Hence, further research is necessary to investigate on the correlation. On the other hand, NHW tumors were most enriched in order *Xanthomonadales*, which also belongs to the phylum *Proteobacteria*. In addition, Smith *et al.* [30] identified an enrichment of family *Streptococcaceae* in triple negative breast cancer and a greater abundance of genus *Bosea* (phylum *Proteobacteria*) that increased with stage.

8. Potential anti-cancer properties of *Sphingomonas yanoikuyae*

Xuan *et al.* [11] have demonstrated that microbial dysbiosis is associated with BC disease state and severity by investigating the breast tumor tissue and paired normal adjacent tissue of the same patient. In the study, *Proteobacteria*, *Firmicutes*, *Bacteroidetes*, *Actinobacteria* and *Verrucomicrobia* formed 96.6% of the microbiota composition. The tumor and paired normal tissue were found to be relatively enriched with the bacteria *Methylobacterium radiotolerans* (100% of samples) and *Sphingomonas yanoikuyae* (95% of samples) respectively [11]. *S. yanoikuyae* was not detected in the corresponding tumor tissue. The presence of *S. yanoikuyae* in normal breast tissue and its significantly lower abundance in corresponding tumor tissue indicates its possible anti-cancer function in the breast [11]. Indeed, *S. yanoikuyae* produces glycosphingolipid ligands, which serve as potent activators of invariant natural killer T (iNKT) cells [88]. These cells are crucial regulators in cancer immunosurveillance [89] and have been shown to have an essential role in controlling BC metastasis [90]. Consequently, the much lower abundance of *S. yanoikuyae* due to dysbiosis could result in reduced bacterial-dependent immune cell stimulation and lead to an environment susceptible to breast tumorigenesis [11]. Hence, further studies are required to explore the potential role of *S. yanoikuyae* in BC which may help to develop preventative strategies and new treatment options for the disease. Moreover, Costantini *et al.* [29] have reported a decrease in relative abundance of *Sphingomonas* in cancerous samples compared to their healthy counterparts in the same patients, substantiating its possible anti-cancer role. Nevertheless, the authors also revealed an increased relative abundance of *Methylobacterium* in the cancerous samples, although these results were not deemed statistically significant as they were not found in all patients of the study. Importantly, the presence of both *Sphingomonas* and *Methylobacterium* genera in *Proteobacteria* phylum was confirmed to be consistent with Xuan *et al.* [11], Urbaniak *et al.* [21] and Wang *et al.* [10].

9. Association between breast cancer invasiveness with *Methylobacterium* and bacterial DNA load

Methylobacterium radiotolerans was found in all samples in Xuan *et al.*'s study [11], but its absolute levels were not significantly varied between tumor and paired normal tissue. This indicates that its higher relative abundance in tumor tissue is resulted from the decrease of other bacteria. The relative abundances of both *S. yanoikuyae* and *M. radiotolerans* were only correlated inversely in paired normal tissue and not in tumor tissue, signifying that dysbiosis is related to BC. Nonetheless, the findings from Wang *et al.* [10] differ from those of Xuan *et al.* [11], whereby the relative abundance of the genus *Methylobacterium* (belonging to the phylum *Proteobacteria*) was significantly lower in breast tissue of BC patients. Although not statistically significant, the relative abundance of *Methylobacterium* in tumor tissue was lower than that of non-cancer control tissue and it was correlated to tumors with greater invasive potential [10]. This suggests that local depletion of the bacterium raises malignant potential. Thus, the abundance of the bacterium may be a potential biomarker for BC diagnosis and staging as well as a possible indicator of prognosis for the disease. Indeed, *Methylobacterium* produces phytohormones such as auxin and cytokinin [91], whereby some of these phytohormones exert anti-cancer effects [92,93]. The difference of the findings between these two studies [10,11] may be due to a multitude of factors, including the methods used in tissue processing, DNA extraction and sequencing. Additionally, Wang *et al.* [10] reported no major shifts between paired normal tissue and invasive carcinoma in microbiomic content or overall diversity, consistent with the findings from Urbaniak *et al.* [24] but in contrast with Xuan *et al.* [11]. The authors also reported that the family *Alcaligenaceae* was more prevalent in cancer compared to non-cancer samples, in which some members of this family are human pathogens such as various species of *Bordetella* and *Achromobacter*, particularly in immunocompromised hosts [94]. Therefore, this may indicate a possible link between these pathogens and BC, which warrants further investigations that could uncover novel mechanisms of breast carcinogenesis.

Moreover, Xuan *et al.* [11] revealed that the amount of bacteria in the healthy breast tissue from healthy controls and paired normal tissue from BC patients were not significantly different in a quantitative analysis of breast microbiota. Nevertheless, the total bacterial DNA load in breast tumor was significantly lower than both of those tissues as determined through quantitative PCR (qPCR) in the analysis. Intriguingly, the bacterial DNA load was also found to be inversely correlated with advanced disease, which could be an additional indicator for the diagnosis and staging of BC. Thus, it can be speculated that a reduction in bacterial DNA load in a healthy individual indicates an increased risk of BC. Furthermore, Xuan *et al.* [11] have found that the basal levels of antibacterial response gene expression were lower in tumor when compared to healthy breast tissue. The significantly lower amount of bacteria in breast tumor tissue compared to paired normal and healthy breast tissues coincides with the decreased expression of one-third of antibacterial response genes examined by Xuan *et al.* [11]. The decreased expression levels of antimicrobial response effectors BPI, IL-12A and MPO as well as innate immune sensors such as TLR 2, 5 and 9 in the tumors indicate the role of bacteria in sustaining healthy breast tissue via stimulation of host inflammatory responses [11].

10. Conflicting role of lactic acid bacteria and *Prevotella* in breast cancer

The lactic acid bacteria (LAB), *Lactococcus* and *Streptococcus* which are more prevalent in the healthy controls from Urbaniak *et al.*'s study [24], may possess anti-carcinogenic properties and could play a role in cancer prevention. *Lactococcus lactis* has been demonstrated to activate murine splenic natural killer (NK) cells and enhances cellular immunity [95]. Increased NK cell activity from peripheral blood mononuclear cells (PBMCs) has been associated with lower cancer risk [96]. Meanwhile, *Streptococcus thermophilus* produces antioxidant metabolites which neutralize peroxide and superoxide radicals, protecting better than other LAB tested against DNA damage induced by reactive oxygen species [97]. Indeed, an epidemiological study demonstrated that women who consume fermented milk products have lower risk of BC, regardless of multivariable risk factors [98]. This protection may be accredited to the health-promoting properties of LAB found in the fermented products. Therefore, the dysbiosis with increased levels of DNA-damaging bacteria and decreased levels of beneficial LAB in BC patients may potentially contribute to the breast carcinogenesis.

Nonetheless, one of the significant ways by which breast microbiota may affect oncogenesis is by increasing the local exposure of breast tissue to estrogen. In Thompson *et al.* [28] study, the most predominant phyla in the tumor samples were *Proteobacteria* (48.0%), *Actinobacteria* (26.3%) and *Firmicutes* (16.2%), consistent with previous findings [11,21,23]. The *Firmicutes* were comprised of 13 substantial species, including the LAB, five *Streptococcus spp.* and two *Lactobaccillus spp.* Prior fecal studies revealed positive associations of the abundance of *Streptococcus* with the presence of β-glucosidase and β-glucuronidase enzymes, which cleave estrogen-glucuronide conjugate and enhance estrogen recirculation [45,99]. Systemic estrogen level is widely known to be implicated with increased BC risk and glucuronidase prevalence has been recently implicated in nipple aspirate fluid of BC survivors [100]. Moreover, Thompson *et al.* [28] found that the expression profiles for the glucuronidase, beta pseudogenes 4 and 9 as well as glucosylceramidase beta 2 were positively linked with *Streptococcus pyogenes*. Increased abundances of *S. pyogenes* and *Lactobaccillus rossiae* were also observed in tumor samples. These evidences suggest that the abundances of LAB are correlated with BC development. Taken together, LAB was shown to possess conflicting roles in breast carcinogenesis and further studies are necessary to validate their roles in the disease.

Interestingly, *Prevotella*, which was more prevalent in healthy controls than in BC patients [24], also has a conflicting association with cancer. *Prevotella* generates, propionate, the short-chain fatty acid which is a beneficial microbial metabolite in the gut that can control colorectal tumor growth [101]. Higher levels of *Prevotella* were found in stool of healthy subjects than those with colorectal cancer in animal and human studies [102,103]. Conversely, higher levels of *Prevotella* is present in the oral cavity of patients with oral squamous cell carcinoma compared to healthy controls. In fact, Mager *et al.* [104] have used *Prevotella* presence as a diagnostic tool and predicted 80% of the cancer cases. Due to the unique microbiota present at each body site, a bacterium may perform differently in a different environment and play different roles at each body site. The conflicting role of *Prevotella* might be due to the metabolites which function differently at different body parts. Therefore, the role of *Prevotella* in breast tissue is yet to be determined. In addition, Urbaniak *et al.* [24] observed similar microbial profiles between normal adjacent tissue and tumor tissue as well as between normal adjacent tissue of the cancer and benign groups. This may indicate the presence of other factors which promotes malignancy and transformation of tumor in cancer patients that are reduced in women with benign tumors, such as higher levels of DNA-damaging bacteria or increased secretion of inflammatory and pro-angiogenic molecules.

11. Future directions

Recent studies have confirmed the presence of microbiota in breast tissue, which was previously thought to be sterile, and provided an insight into the association between the microbiota and BC. However, the investigation of breast microbiota in BC patients is still in its infancy and future studies involving a larger sample size are required to validate these findings. Although the human microbiota may be specific in each individual, the human population shares a phylogenetic core formed by certain species of bacteria such as the commonly abundant phyla *Proteobacteria* and *Firmicutes* identified in breast tissue from different studies (Table 1). After validating the findings on breast microbiota, further research is necessary to determine the functional roles of bacteria which are differentially abundant in the breast tissue of patients with BC, benign tumors as well as healthy individuals. Some of the bacteria have been found to possess pro-carcinogenic properties and promote breast carcinogenesis, while others may protect against BC through their beneficial health effects. Indeed, a greater relative abundance of bacteria which caused DNA damage *in vitro* as well as a decrease in LAB which possess anti-carcinogenic properties were detected in BC patients, suggesting a potentially important role of breast microbiota in modulating the risk of the disease [24]. Nonetheless, it is possible that the healthy and diseased states are not driven by a single organism but an interplay of polymicrobial interactions.

Different bacterial signatures may be found in breast tissues of patients with different BC subtypes. In fact, bacterial signatures and information of the microbiota, such as bacterial DNA load, have been associated with BC invasiveness and could potentially be used in screening and diagnosis of the disease [11]. Additionally, examining other aspects of the breast microbiota, including bacterial metabolites as well as bacterially induced host metabolites could offer crucial information on breast health. Meanwhile, previous studies have shown that bacteria maintain breast health by stimulating resident immune cells [11] and thus, the effect of immunology in breast health should be further investigated. Notably, microbiota has also been found to affect the efficacy and toxicity of cancer treatments [60]. This signifies a novel strategy to exploit the microbiota to improve efficacy and reduce toxicity of cancer therapies. Importantly, by exploiting the knowledge on breast microbiota, preventative strategies or treatments can be implemented through modulation of the microbiota to create a less hospitable environment for cancer. This can be done through antibiotics which targets pro-carcinogenic bacteria as well as prebiotics or probiotics that protect against BC. Hence, this could serve as an adjuvant treatment or alternative to the existing cancer therapies, which have caused many undesirable side effects, to improve the prognosis and quality of life of BC patients. However, it was also found that antibiotics impact the microbiota, which in turn affect the efficacy of cancer therapies as well as the risk and recurrence of BC [70,75-79]. Therefore, any antibacterial therapy changing the microbiota equilibrium during the use of cancer therapy needs to be carefully assessed. In fact, depending on the composition and prevailing species of the heterogenous microbiota in patients, it can either be beneficial or detrimental to tumor progression and therapy. Hence, a personalized approach based on specific microbiota composition of the patients may be necessary in the future and further investigations on this aspect would be required.

It remains unclear whether the bacterial profile differences are the consequence or cause of BC, which may require the use of germ-free animal models to reveal its role, although there has been evidence in favor of the latter in other diseases. Animal studies involving fecal transplants from those with colorectal cancer, colitis or obesity have caused the development of these diseases in healthy

animals [103,105,106]. In addition, current studies on breast microbiota utilized a wide range of patient populations, sample processing, extraction techniques, amplification primers, sequencers and bioinformatics pipelines. Hence, it may be difficult to compare between the studies and further investigations are needed to determine which associations are strong enough to proceed with the following functional research. Interestingly, geographical and racial differences have been shown to influence breast tissue microbiota and correlate with BC [21,30]. Therefore, it may be valuable to explore further on these factors to establish the correlation which could potentially improve preventative and treatment strategies for the disease. Currently, various hypervariable regions of the 16S-rRNA gene, including V2, V3, V4, V6+7, V8 and V9 have been examined in breast microbiota studies. Importantly, Costantini *et al*. [29] have determined that the V3 region is the most informative compared to other regions for breast tissue microbiota. Thus, prioritizing the V3 region in future breast tissue microbiota studies may yield more information. In addition, the findings from the recent studies are potentially confounded by the effects of menopausal status, BMI, age and race of the human subjects. Therefore, clinically matched patients would provide more accurate analyses of the findings. Additionally, studies investigating the microbiota from other body sites, such as the gut, urinary tract, oral cavity and skin may identify other bacterial signatures which could serve as non-invasive biomarkers for diagnosis and aid in the development of BC treatments. It is also important to note that these much highlighted changes may interact with the breast microbiota to promote the health of the breast or act in concert to orchestrate BC development. Hence, this warrants further investigations to allow better understanding of the body-wide impacts of microbiota on BC.

12. Conclusions

Recent studies have shed light upon the relationship between breast microbiota and BC, whereby microbial dysbiosis is associated with the disease. Microbial signatures have been identified in the breast microbiota whereby certain bacterial species were found to possess pro-carcinogenic and/or anti-carcinogenic properties. Intriguingly, studies have also found correlation between breast tissue microbiota and other factors, such as geographical and racial differences, in BC. Furthermore, breast microbiota has been found to impact efficacy and toxicity of cancer treatments as well as the risk and recurrence of BC. Nonetheless, the study of breast microbiota and its association with BC is still in its infancy. Moving forward, further unravelling of the functionality of the microbial signatures would allow better understanding of its role in breast carcinogenesis and enable the development of screening tests, preventative strategies, diagnostic tools as well as treatments for BC.

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