



The involvement of oncobiosis and bacterial metabolite signaling in metastasis formation in breast cancer

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Abstract

Breast cancer, the most frequent cancer in women, is characterized by pathological changes to the microbiome of breast tissue, the tumor, the gut, and the urinary tract. Changes to the microbiome are determined by the stage, grade, origin (NST/lobular), and receptor status of the tumor. This year is the 50th anniversary of when Hill and colleagues first showed that changes to the gut microbiome can support breast cancer growth, namely that the oncobiome can reactivate excreted estrogens. The currently available human and murine data suggest that oncobiosis is not a cause of breast cancer, but can support its growth. Furthermore, preexisting dysbiosis and the predisposition to cancer are transplantable. The breast's and breast cancer's inherent microbiome and the gut microbiome promote breast cancer growth by reactivating estrogens, rearranging cancer cell metabolism, bringing about a more inflammatory microenvironment, and reducing the number of tumor-infiltrating lymphocytes. Furthermore, the gut microbiome can produce cytostatic metabolites, the production of which decreases or blunts breast cancer. The role of oncobiosis in the urinary tract is largely uncharted. Oncobiosis in breast cancer supports invasion, metastasis, and recurrence by supporting cellular movement, epithelial-to-mesenchymal transition, cancer stem cell function, and diaporesis. Finally, the oncobiome can modify the pharmacokinetics of chemotherapeutic drugs. The microbiome provides novel leverage on breast cancer that should be exploited for better management of the disease.

Keywords Breast cancer · Oncobiome · Oncobiosis · Inflammation · Metastasis · Bacterial metabolite

1 Introduction

Dysbiosis is an abnormal adaptation of the microbiome, characterized by abnormal microbial composition and function. Neoplastic diseases are characterized by dysbiosis that is coined oncobiosis [1]. The microbiome that is undergoing oncobiome transformation is termed the oncobiome. Oncobiosis occurs in multiple neoplasias, including breast cancer, and oncobiosis may have a pathogenic role in these cancers [2–8]. In this review, we will dissect the microbiome-elicited

pathways and discuss how these pathways protect against metastasis formation in breast cancer.

Breast cancer is the most frequent cancer among women and is the leading cause of cancer-related deaths in women [9, 10]. Nevertheless, in developed countries, the 5-year survival of breast cancer is above 80% due to population-wide screening programs and the consequent early identification [11]. Although several risk factors were identified that increase the risk for breast cancer, most newly diagnosed patients have no obvious risk factors [12]. The risk for breast cancer increases with age, and most breast cancer patients are diagnosed in their 50 s after menopause. Extended exposure to female hormones due to hormone-replacement therapy, early menarche, and late menopause are risk factors for breast cancer [12]. BRCA1 and BRCA2 genes were identified as genetic risk factors for breast cancer, although mutation carriers represent a minority among breast cancer patients [13]. A family history of breast cancer or neoplasias is also a risk factor for breast cancer [12] and dense breast [14, 15]. Successful pregnancies, lactation, and physical activity are protective factors against the disease

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[12, 16]. For further information, we refer the readers to the relevant guidelines [17–20]. We reference the latest versions of the guidelines. Nevertheless, we ask the readers to check whether the guidelines were updated at the time our paper is being read.

2 Oncobiosis in breast cancer

The first mention of the possible pathological role of the oncobiome in breast cancer dates back to 1971 [21]. The causative role of oncobiosis in the pathogenesis of breast cancer is underscored by the observations that antibiotic use increases the risk for breast cancer in mice [22–24], and the majority of studies suggest an increased risk in humans, also [25–33] (it should be noted that [34] and [35] found no association between antibiotic exposure and breast cancer risk). In further support of the pathological role of the microbiome, prebiotics [36], probiotics [37–45], and diverse nutrition [46–49] reduce the risk of breast cancer. Furthermore, risk factors of breast cancer, such as high-density breast [50], early menarche [51], low physical activity [51], increases in BMI [51, 52], age [53], and alcohol consumption [54], are also associated with microbiome changes culminating in breast cancer-associated oncobiosis.

Multiple microbial compartments undergo oncobiome transformation during breast cancer, including breast tissue [55, 56], milk ducts [57], the inherent microbiome of the breast carcinoma [54, 58–72], the distal gut [51, 52, 73–89], and the urinary microbiome [54, 90]. However, no differences in the microbiome of the nipple [57, 69] and the oral microbiome [54] between healthy individuals and breast cancer patients have been detected. Besides bacteria, viruses (parapoxviruses [91], human papillomavirus [92], Herpesviridae, Retroviridae, Parapoxviridae, Polyomaviridae, Papillomaviridae [64]), fungi, and parasites were identified in breast cancer tissue [64, 65, 70], although these signatures are not ubiquitous in all individuals. Of note, microbiome signatures in the oncobiome correlate with survival in breast cancer, which underlines the importance of oncobiome transformation in regulating breast cancer behavior [70]. The microbiome is now considered a component of the tumor microenvironment [93].

In the following chapters, we will discuss changes in the microbiome of different compartments. In each compartment, the results can be contradictory, so we identified common elements that are discussed in the chapters discussing the respective compartments. The findings of the individual studies are assembled in Table 1. The bilateral mechanistic connections between the host and the microbiome [94] and

oncobiome support of cancer cells (Fig. 1) are discussed in the following chapters.

3 Interactions between the oncobiome, tumors, and tumor cells

3.1 Tumor colonization

The breast tissue has its own microbiome that has higher diversity than that of the vagina, but has lower diversity than that of the oral cavity or the gut [96]. The microbiomes of the breast skin and the inner breast tissues are different [56]. The microbiome of the exterior surface of the breast (e.g., the nipple) does not change in breast cancer [57]. Nevertheless, the composition of the microbiome of the milk ducts changes in the presence of a malignant process, evidenced in nipple aspirates [57].

Next-generation sequencing methods identified bacterial DNA in breast tumors [66] that was confirmed later by alternative methods [64, 65, 67]. Breast tumor has a higher bacterial load than melanoma, lung tumors, ovarian cancer, and glioblastoma and has similar counts to pancreas and bone cancers [67]. The carcinoma tissue is colonized by bacteria [54, 58–60, 62, 65, 67, 68, 70], and differences were detected among the subtypes of breast cancer as a function of hormone receptor status [54, 59, 60, 63–65, 70], HER2 receptor status [65], invasiveness [54], grade [54, 58, 60, 66, 70], stage [59, 60, 70], and immunological signatures [60]. Tumor-associated bacteria are culturable and class among *Proteobacteria*, *Firmicutes*, and *Actinobacteria* [67]. In a fraction of breast cancer cases, intracellular and perinuclear bacteria were identified [67]. Furthermore, fungi, parasites, and viruses [64, 70, 91, 92] were detected in tumor tissue. Racial differences were identified in the breast tissue and tumor microbiome [59, 63]. Of note, certain components of the intratumoral and tissular microbiome correlate with patient survival [70].

What are the functional contributions of the breast microbiome to tumorigenesis and tumor progression? As LPS+, Gram negative bacteria were detected intratumorally [67], intratumoral bacteria likely have a key role in the local immune response (see in a later chapter). In agreement with this concept, the expression of bacterial LPS biosynthetic genes were upregulated in nipple fluid aspirate [57]. Lipoteichoic acid (LTA), a marker for Gram positive bacteria, was absent in breast cancer [67].

Imputed pathway analysis revealed relevant functions for the breast microbiome (Table 2). As with other features, there are discrepancies between the studies. Nevertheless, the identified pathways can be classified into logical categories that can be linked to tumorigenesis. Furthermore,

Table 1 Changes to the gut microbiome in breast cancer

Patient cohort Mode of analysis	Changes to the microbiome, biomarker observations, diversity	Reference
Changes to the breast tissue microbiome		
Breast tissue obtained from surgery of benign tumors ($n = 13$), cancerous ($n = 45$), and healthy breast tissue ($n = 23$) 16S rRNA gene sequencing	The bacterial composition of the healthy breast tissue and breast cancer tissue is different. Higher abundances of <i>Prevotella</i> , <i>Lactococcus</i> , <i>Streptococcus</i> , <i>Corynebacterium</i> , and <i>Micrococcus</i> in healthy breast tissue and <i>Bacillus</i> , <i>Staphylococcus</i> , unclassified <i>Enterobacteriaceae</i> , unclassified <i>Comamonadaceae</i> , and unclassified <i>Bacteroidetes</i> in breast cancer tissue	[55]
15 malignant cancer (stages I and II) and 13 benign atypia patients 16S rRNA gene sequencing	No significant differences in alpha diversity values, but beta diversity differs between the breast tissue of malignant and benign breast tissue. <i>Fusobacterium</i> , <i>Atopobium</i> , <i>Hydrogenophaga</i> , <i>Gluconacetobacter</i> , and <i>Lactobacillus</i> abundance increased in the tissue of the malignant cases	[56]
141 breast tissue samples from BC patients	Enterococcus abundance plays a vital role in regional recurrence	[95]
Changes to the milk duct microbiome		
Nipple aspirate fluid from breast cancer surviving patients ($n = 6$) and healthy controls ($n = 9$) 16S rRNA gene sequencing	Beta diversity, but not the alpha diversity, is different between breast cancer patients and healthy controls. <i>Alistipes</i> was present only in the nipple aspirate from breast cancer patients, while unclassified <i>Sphingomonadaceae</i> genus was enriched in the nipple aspirate of healthy controls	[57]
Changes to the breast carcinoma microbiome		
Percutan needle biopsy from 22 benign and 72 malignant breast cancer patients 16S rRNA gene sequencing	Slightly higher alpha diversity in patients with malignant disease. <i>Proteobacteria</i> increased in malignant cases. The genus <i>Propionimonas</i> and the families <i>Micrococaceae</i> , <i>Caulobacteraceae</i> , <i>Rhodobacteraceae</i> , <i>Nocardioideaceae</i> , and <i>Methylobacteriaceae</i> increased in the malignant disease group	[58]
8 normal breast tissues, 64 breast tumors, in 11 cases paired non-cancerous adjacent tissue 16S rRNA gene sequencing	Alpha diversity and beta diversity indices were lower in the tumor tissue. <i>Clostridia</i> , <i>Bacteroidia</i> , <i>WPS_2</i> , <i>Ruminococcaceae</i> , <i>Fusobacteria</i> , and <i>Spirochetes</i> increased, while <i>Pseudomonadaceae</i> , <i>Sphingomonadaceae</i> , <i>Caulobacteraceae</i> , <i>Thermi</i> , and <i>Actinobacteria</i> decreased in tumors. <i>Streptococcaceae</i> and <i>Ruminococcus</i> were abundant in TNBC tumors; <i>Xanthomonadales</i> in Luminal A; <i>Clostridium</i> in Luminal B; <i>Akkermansia</i> , <i>Ruminococcaceae</i> and genus <i>Hyphomicrobium</i> were more abundant in stage I Her2+ tumors, <i>Sporosarcina</i> in stage II, <i>Bosea</i> in stage III+IV	[59]
221 breast cancer specimens, breast tissue from 18 individuals predisposed to breast cancer, and 69 controls 16S rRNA gene sequencing	Alpha diversity values were lower in tumors and the breast tissue of the risk population. Widespread association with stage, lobular or ductal origin, and hormone receptor positivity	[60]
Cancerous tissue and adjacent healthy tissue from 16 breast cancer patients 16S rRNA gene sequencing	No significant differences in alpha diversity. No difference between the cancerous and the adjacent healthy tissues	[61]
BC tumor and adjacent normal tissue from 6 + 10 TNBC WNH and 7 TNBC BNH, 7 TPBC WNH, and 3 TPBC BNH 16S rRNA gene sequencing	In triple-positive and triple-negative breast cancer from black non-Hispanic alpha indices decrease, in white non-Hispanic women alpha indices increase <i>Fusobacteria</i> and <i>Streptococcus</i> abundance increase in the tumor. There is a difference between the microbiome composition of triple-positive and triple-negative breast cancers	[63]
10 archived breast cancer tumor tissue, 10 freshly excised normal breast tissue, 8 of them from both breasts 16S rRNA gene sequencing	<i>Ruminococcaceae</i> , <i>Akkermansia</i> , <i>Verrucomicrobia</i> increased, while <i>Sutterella</i> , <i>Acinetobacter</i> , <i>Bacteroides</i> , <i>Cyanobacteria</i> , <i>Proteobacteria</i> , <i>Synergistetes</i> , and <i>Tenericutes</i> decreased in the tumor tissue. Alpha index decreased in the tumor tissue	[62]

Table 1 (continued)

Patient cohort Mode of analysis	Changes to the microbiome, biomarker observations, diversity	Reference
44 BC patients and 20 controls. Significant age and body mass index difference between cohorts	No significant difference in alpha diversity. <i>Methylobacterium</i> decreased in cancer patients and was drastically reduced when invasion was reported. In cancer patients, levels of gram-positive organisms including <i>Corynebacterium</i> , <i>Staphylococcus</i> , <i>Actinomyces</i> , and <i>Propionibacteriaceae</i> increased	[54]
16S rRNA gene sequencing		
100 TNBC, 17 matched, 20 non-matched controls PathoChip technology	Higher association of <i>Brevundimonas diminuta</i> , <i>Arcanobacterium haemolyticum</i> , <i>Pep-toniphilus indolicus</i> , <i>Prevotella nigrescens</i> , <i>Propionibacterium jensenii</i> , and <i>Capnocytophaga canimorsus</i> and a set of viruses and fungi are associated with TNBC samples compared to normal tissues	[64]
50 BRER, 34 BRHR, 24 BRTP, 40 TNBC, 20 controls PathoChip technology	BRER is characterized by <i>Arcanobacterium</i> , <i>Bifidobacterium</i> , <i>Cardiobacterium</i> , <i>Citrobacter</i> , and <i>Escherichia</i> species; BRTP is characterized by <i>Bordetella</i> , <i>Campylobacter</i> , <i>Chlamydia</i> , <i>Chlamydophila</i> , <i>Legionella</i> , and <i>Pasteurella</i> ; BRHR is characterized by <i>Streptococcus</i> ; TNBC is characterized by <i>Arcobacter</i> , <i>Geobacillus</i> , <i>Orientia</i> , and <i>Rothia</i>	[65]
Healthy (age-matched) ($n = 23$), paired normal ($n = 39$), and tumor tissue ($n = 39$) 16S rRNA gene sequencing	Bacterial copy number decreased in tumors and with increased grade. <i>Sphingomonadaceae</i> family, <i>Sphingomonas</i> species decreased, while the <i>Methylobacteriaceae</i> family, <i>Methylobacterium</i> species increased in tumors	[66]
668 breast tumor and 72 non-cancerous breast tumor sequences from the TCGA data portal	<i>Salmonella enterica</i> , <i>Escherichia coli</i> , <i>Bacillus alcalophilus</i> , <i>Brachybacterium muris</i> , <i>Plesonius fermentans</i> , <i>Mycobacterium phlei</i> , and <i>Acinetobacter radioresistens</i> increased, while <i>Microbacterium barkeri</i> , <i>Acinetobacter baumannii</i> , <i>Ralstonia pickettii</i> , <i>Lactobacillus rossiae</i> , and <i>Mycobacterium fortuitum</i> decreased in the tumors	[68]
256 normal tissue and 355 breast tumors	Bacterial LPS and 16S RNA were detected in breast cancer cells in breast tumors. The microbiome of the breast tumors was richer than other tumors assessed and in normal adjacent breast tissue. <i>Proteobacteria</i> , <i>Firmicutes</i> , and <i>Actinobacteria</i> can be found in breast tumors. Differences in ER+ and ER- breast tumors	[67]
21 female and 2 male BC patients 16S rRNA gene sequencing	Compared to normal breast tissue, the abundance of <i>Proteobacteria</i> increased in tumor tissue	[69]
95–105 FFPE samples for each BC subtype, 86 controls PathoChip	Large set of viruses, parasites, and fungi were detected in FFPE sections of breast cancer. The least of these were detected in TNBC cases	[70]
16 healthy controls, 32 breast cancer patients 16S rRNA gene sequencing	The abundance of <i>Corynebacterium</i> , <i>Prevotella</i> , and <i>Gamma</i> proteobacteria (unclassified) decreased, while <i>Acinetobacter</i> increased in BC tissue	[71]
Changes to the gut microbiome		
48 postmenopausal BC patients (most stages 0–I), vs. 48 control patients 16S rRNA gene sequencing	Breast cancer patients had a higher abundance of <i>Clostridium</i> , <i>Faecalibacterium</i> , and <i>Ruminococcus</i> (all <i>Clostridiales</i>) and a lower abundance of <i>Dorea</i> and <i>Lachnospiraceae</i>	[73]
30 BC and 36 control patients Classical bacterial culture	Lower number of observed species, Chao I and PD whole tree indices in breast cancer patients Fecal bile acid levels were lower in breast cancer patients. Bacterial nuclear dehydrogenating activity increased in breast cancer patients suggesting increases in <i>Clostridia</i> abundance in feces	[82]
18 premenopausal BC patients, 25 premenopausal controls, 44 postmenopausal BC patients, 46 postmenopausal healthy controls Comprehensive shotgun sequencing	Species number, chao I, and JSD values were higher in postmenopausal cancer patients than in controls. Widespread taxonomical changes in BC patients	[75]

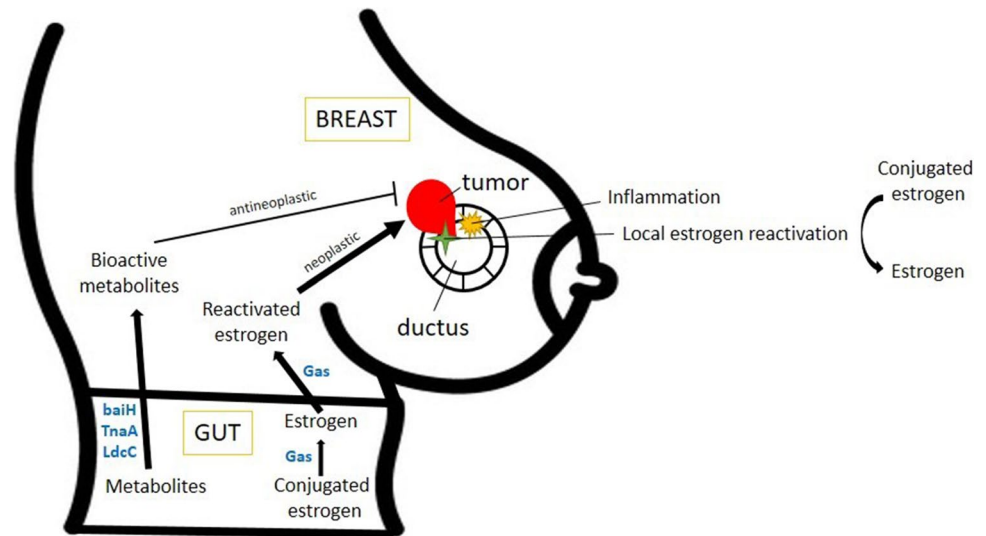
Table 1 (continued)

Patient cohort Mode of analysis	Changes to the microbiome, biomarker observations, diversity	Reference
379 BC patients, 102 non-malignant breast disease, 414 population-based controls 16S rRNA gene sequencing	Alpha diversity indices correlate negatively with the odds for BC, BC grade, and subtype. No difference in the microbiome of malignant and non-malignant patients, but differ when compared to controls. Bacteroides, Flavonifractor, and Ruminococcaceae strongly and positively associated with BC, while Romboutsia, Coprococcus 2, Christensenellaceae R-7 group, Dorea, [Eubacterium] coprostanoligenes group, Pseudobutyribrio, and Lachnospira negatively associated with BC	[74]
32 overweight stage 0–II BC patients 16S rRNA gene sequencing	Akkermansia high abundance patients had higher alpha diversity compared to low abundance patients	[52]
31 female BC patients 16S rRNA gene sequencing	Total bacterial count decreased in overweight patients. The abundance of Firmicutes, Faecalibacterium prausnitzii, Blautia sp., and Eggerthella lenta decreased in overweight patients. Blautia sp. abundance increased as a function of tumor grade. Bacteroides, Clostridium coccoides, Clostridium leptum, Faecalibacterium prausnitzii, and Blautia sp. increased in stage II–III patients compared to stage 0–I patients	[77]
37 incident BC patients 16S rRNA gene sequencing	Early menarche patients had lower Chao1 and OTU indices and lower Firmicutes abundance. Lower OTU, Chao1, and Shannon indices; lower Blautia, Coprococcus, Ruminococcus, and Oscillospira; and higher Firmicutes abundance in Her2 – cases compared to Her2 + cases. Clostridium and Veillonella increased in grade III patients. High total body fat was associated with lower Chao1 and OTU indices	[51]
48 postmenopausal BC case patients (most stages 0–I), vs 48 control patients (same as [73]) qPCR of specific loci	Abundance of DNA coding for the baiH gene of Clostridium ordelli, Bacteroides thetaiotaomicron, Escherichia coli, Pseudomonas putida, and Staphylococcus haemolyticus decreased in breast cancer patients, the most pronounced changes were detected in situ carcinoma patients	[78]
48 postmenopausal BC case patients (most stages 0–I), vs 48 control patients (same as [73]) qPCR of specific loci	Abundance of DNA coding for the CadA gene of Escherichia coli and the LdcC gene of Escherichia coli, Enterobacter cloacae, and Hafnia alvei decreased in breast cancer patients, the most pronounced changes were detected in situ carcinoma patients	[79]
3 control and 4 stage I BC patients Western blotting	Fecal expression of Escherichia coli LdcC protein was lower in stage I patients	
48 postmenopausal BC case patients (most stages 0–I), vs 48 control patients (same as [73]) qPCR of specific loci	Abundance of DNA coding for the TnaA gene of Alisipipes shahii, Providencia rettgeri, Bacteroides xylanisolvens, and Clostridium sp. decreased in breast cancer patients, the most pronounced changes were detected in situ carcinoma patients	[80]
35 BC patients Western blotting	Fecal expression of Escherichia coli TnaA was higher in patients with tumor-infiltrating lymphocyte (TIL) ratio over 20% compared to that of those below. Fecal E. coli TnaA expression correlated with TIL percentage	
35 BC cases Western blotting	Fecal expression of TnaA Escherichia coli LdcC protein was lower in lobular cases	[81]
48 postmenopausal BC cases, 48 control 16S rRNA gene sequencing	Lower alpha diversity in breast cancer patients. Lower alpha diversity among IgA-coated bacteria	[83]
124 BC survivor patients 16S rRNA gene sequencing	Abundance of Actinobacteria (Bifidobacterium) was associated with increased levels of DHA. Abundance of Bacteroidetes negatively correlated with EPA levels that were abrogated in patients receiving chemotherapy	[85]

Table 1 (continued)

Patient cohort Mode of analysis	Changes to the microbiome, biomarker observations, diversity	Reference
30 controls vs. 25 BC cases 16S rRNA gene sequencing	In breast cancer patients, Bacteroidetes phylum, <i>Clostridium</i> cluster IV, <i>Clostridium</i> cluster XIVa, and <i>Blautia</i> sp. decreased, and Firmicutes phylum increased. No difference in the total number of bacteria. Alpha diversity increased in patients	[84]
200 BC patients (stages I–II) and 67 controls 16S rRNA gene sequencing	Alpha diversity lower in premenopausal patients, no difference in the postmenopausal cohort; beta diversity is different. Bacteroidetes proportions increased in BC patients	[87]
76 BC patients (35 stage II/III, 21 stage I), 336 healthy volunteers Comprehensive shotgun sequencing	52 units, mostly at the species level, decreased, while 38 units increased in breast cancer patients compared to healthy volunteers. 11 species increased in stage II/III patients, while 21 species increased in stage I patients	[86]
83 invasive BC patients, 19 patients with benign breast tumors 16S rRNA gene sequencing	No difference in alpha and beta diversity indices. The abundance of <i>Clostridium</i> , Faecalibacterium, Lachnospira, Erysipelotrichaceae, Romboutsia, Fusicatenibacter, Xylophilus, and Arcanobacterium decreased, while the abundance of <i>Citrobacter</i> increased in malignant BC patients. Distinct patterns identified BC subtypes and a microbial pattern associated with highly proliferative tumors	[89]
Changes to the urinary microbiome		
44 BC patients and 20 controls. Significant age and body mass index difference between cohorts 16S rRNA gene sequencing	Cancer patients had significantly higher Shannon index. Peri/postmenopausal urinary microbiome had higher Shannon index compared to premenopausal samples. <i>Corynebacterium</i> , <i>Staphylococcus</i> , <i>Actinomyces</i> , and <i>Propionibacteriaceae</i> abundance increased in cancer patients	[54]
220 controls and 127 BC patients 16S rRNA gene sequencing of the bacterial extracellular vesicles	The abundance of <i>Bacteroides</i> and <i>Ruminococcaceae</i> -derived extracellular vesicles were higher in the breast cancer group, while <i>Clostridiales</i> and <i>Pseudomonas</i> -derived extracellular vesicles were more abundant in healthy controls	[90]
Abbreviations: <i>BRHR</i> , human epidermal growth factor receptor 2 positive; <i>BMI</i> , body mass index; <i>BNH</i> , African American as Black non-Hispanic; <i>BRER</i> , estrogen or progesterone receptor positive; <i>BRTP</i> , estrogen, progesterone, and HER2 receptor positive; <i>EPA</i> , eicosapentaenoic acid; <i>FFPE</i> , formalin-fixed paraffin-embedded; <i>HER2</i> , epidermal growth factor receptor 2; <i>IDC</i> , invasive ductal carcinoma; <i>ILC</i> , invasive lobular carcinoma; <i>yrs.</i> , years; <i>TIL</i> , tumor-infiltrating lymphocyte; <i>TNBC</i> , triple-negative breast cancer; <i>TPBC</i> , triple-positive breast cancer; <i>rRNA</i> , ribosomal RNA; <i>WNH</i> , White non-Hispanic		

Fig. 1 Oncobiosis supports breast carcinogenesis in a multi-pronged fashion. Abbreviations are in the text



certain predicted metabolic pathways are similar to the pathway associated with carcinogenesis in breast tissue [62].

DNA coding for beta-glucuronidase enzymes (KEGG ortholog Beta-Glucuronidase K01195), responsible for conjugated estrogen reactivation, was elevated in the nipple aspirate fluid from breast cancer patients [57], suggesting a possible local reactivation of estrogens. In patients, *Roseburia*, *Rikenellaceae*, *Bacteroides uniformis*, *Paenibacillus amylolyticus*, and *Ellin6075* were the OTUs contributing to increased beta-glucuronidase abundance [57]. The same study showed an increase in the abundance of genes coding for steroid hormone biosynthesis [57].

Breast cancer cells are characterized by lower oxidative stress than the parent terminal lobular-ductal unit (TLDU) tissue [97]. The low level of oxidative and nitrosative stress is a key feature of successful tumor growth [98, 99]. Tissular and intratumor bacteria can support low tumoral oxidative and nitrosative stress by upregulating L-ascorbate biosynthesis II (L-glucose pathway) [67]. This is further strengthened by increased mycothiol biosynthesis in ER + tumors [67]. Mycothiol is used by bacteria to detoxify reactive oxygen species [100]. In addition to oxidative/nitrosative stress, the physical presence of bacteria can also induce DNA damage, at least in part, due to the overexpression of colibactin [55]. Among *Enterobacteriaceae*, *Escherichia coli* or *Staphylococcus* can produce a toxin, colibactin [55, 101, 102]. In agreement with this concept, Klann and colleagues [62] demonstrated a correlation between the expression of base excision repair genes and the bacterial colonization of the breast tissue.

Metabolic changes were described in the imputed pathway analyses. Of note, some reports show contradictory results. Changes affect core metabolic pathways, including anaerobic respiration [67], oxidative phosphorylation [57], and central carbon metabolism [62]; stage I tumors were

enriched in genes of energy metabolism [59]. Another set of changes affected lipid metabolites, such as sphingolipid metabolism [57], synthesis and degradation of ketone bodies [57], linoleic acid biosynthesis [57], and choline metabolism [62]. In benign cases, fatty acid biosynthesis and branched dibasic acid metabolism increased [56], while in stage I tumors, genes of fat digestion and absorption were enriched [59]. A large set of amino acid metabolic pathways were affected (tryptophan glycine, serine, threonine, phenylalanine biosynthesis [57]), as well as nitrogen metabolism [57]. In benign cases, cysteine and methionine metabolism genes were enriched [56]. Changes were described in detoxification processes, such as polycyclic aromatic hydrocarbon degradation [57] and benzoate degradation [57] in the onco-biome. In malignant cases, local, oncobiome-mediated drug metabolism may increase [56]. Interestingly and importantly, signal transduction pathways such as PI3K-Akt [62], HIF-1 [62] and the AMPK pathway [62], microRNAs involved in carcinogenesis [62], and inositol phosphate metabolism [56] changed in the breast cancer oncobiome. In stage 2 tumors, the microbiome was enriched in phosphotransferase system protein genes [59]. Furthermore, sulfur metabolism genes changed in the breast cancer oncobiome [57] and glycosyltransferases increased in benign cases [56]. Breast cancer is characterized by changes in cell metabolism that is actionable for disease treatment and management [103–112]. Furthermore, the intricate supportive metabolic circuit between cancer cells and non-cancerous stroma cells can facilitate tumor growth and lead to worse clinical outcomes [103–105, 113]. Giallourou and colleagues [71] showed that breast bacteria interfere with the biosynthesis of ceramide, cholesterol, oxidized cholesteryl esters, diacylglycerol, lysophosphatidylcholine, phosphatidylethanolamines, and phosphatidylcholines to modulate the lipid composition of tumors. Of note, cholesterol and lipid homeostasis also play a role

Table 2 Changes to the function of the onco biome in breast cancer deduced from imputed pathway analyses

Bacterial pathway	Study
Stage I tumors were enriched in energy metabolism, fat digestion, and absorption	[59]
Stage II tumors are enriched in phosphotransferase system proteins	
Increased in benign cases:	[56]
Cysteine metabolism	
Methionine metabolism	
Glycosyltransferases	
Fatty acid biosynthesis	
Branched dibasic acid metabolism	
Increased in malignant cases:	
Drug metabolism (other enzymes)	
Inositol phosphate metabolism	
Upregulated in breast cancer cases:	[67]
Dermatan sulfate degradation	
Indole acetate biosynthesis	
L-ascorbate biosynthesis II (L-glucose pathway)	
Mycothiol biosynthesis	
Upregulated in breast cancer cases:	[55]
Colibactin biosynthesis	
Upregulated in breast cancer cases:	[57]
Flavone and flavonol biosynthesis (incl. beta-glucuronidase)	
Isoflavonoid biosynthesis	
Flavonoid biosynthesis	
Steroid hormone biosynthesis	
Synthesis and degradation of ketone bodies	
Tryptophan metabolism	
Sulfur metabolism	
Lipopolysaccharide biosynthesis	
Sphingolipid metabolism	
Polycyclic aromatic hydrocarbon degradation	
Glycine, serine, and threonine biosynthesis	
Oxidative phosphorylation	
Benzoate degradation	
Phenylalanine biosynthesis	
Peptidoglycan biosynthesis	
Linoleic acid biosynthesis	
Nitrogen metabolism	
Upregulated in breast cancer cases:	[62]
Base excision repair	
Th17 cell differentiation	
Choline metabolism	
Central carbon metabolism	
Necroptosis, microRNAs involved in carcinogenesis	
Proteoglycans involved in carcinogenesis	
Signaling pathways including IL-17, PI3K-Akt, HIF-1, and AMPK	

[4, 114–116]. The widespread changes to the onco biome metabolism suggest that the breast cancer onco biome participates in the metabolic support of rapidly dividing breast cancer cells.

In terms of cell death and cell division, the breast cancer onco biome is associated with necroptosis [62]. *Haemophilus influenzae* is associated with mitotic spindle formation and G2M checkpoint regulation [68]. The breast cancer onco biome is also associated with movement and metastasis-related processes, such as dermatan sulfate degradation [67], peptidoglycan biosynthesis [57], and proteoglycan homeostasis [62]. *Listeria fleischmannii* in the breast cancer onco biome is associated with epithelial-to-mesenchymal transition [68].

Tzeng and colleagues have shown that elements of the microbiome covaried with different markers of bad clinical outcomes. Namely, *Staphylococcus* negatively covaried with *TRAF4*, *Pelomonas* positively covaried and *Bradyrhizobium* negatively covaried with VEGF-A, and *Propionibacterium* negatively covaried with PDGF-AA and PDGF-BB. In addition to these data, circumstantial data suggest bacterial secretory proteins [41] are probably also involved in communication between the microbiome and tumor tissue.

3.2 Bacterial metabolite signaling and the onco biosis of the gastrointestinal tract and urinary tract

The gut microbiome undergoes onco biotic transformation in breast cancer [21, 51, 52, 73–82]. In terms of diversity indices, Goedert and colleagues [73] and Byrd and colleagues [74] reported lower or trends towards lower diversity indices in three different cohorts, while Zhu and colleagues [75] and Bobin-Dubigeon and co-workers [84] reported increased alpha diversity indices. Howe and co-workers [76] reported increases in alpha diversity indices in a Pten-deficient mouse model backing the observations of Zhu and colleagues [75] and Bobin-Dubigeon and co-workers [84]. No differences in alpha diversity were reported in [87] and [89]. However, the multiple observations make lower alpha diversity more likely. As noted earlier, risk factors for breast cancer lead to decreases in diversity, such as high-density breast [50], early menarche [51], low physical activity [51], and increases in BMI [51, 52]. Furthermore, antibiotic overdose, which leads to lower diversity, increases the risk for breast cancer [22, 23, 25–32], while probiotics that increase diversity have a protective effect [37–45].

Characteristic changes in the microbiome were observed between clinical stages [51, 77–79, 81] and grades [51, 89], MIB positivity [51], receptor status [51, 89], and proliferative capacity [89]. The most drastic changes were observed among in situ carcinoma and stage I patients, which were gradually rediversified in subsequent stages [77–79, 81]. Characteristic changes in taxa between patients and controls

include *Clostridiales* [51, 73, 77, 82], *Blautia* [51, 77], and *Akkermansia muciniphila* [52, 76].

The gut microbiome is distant from the breast tumor; hence, signaling pathways are needed to connect the two distant compartments. Multiple pathways cross-connect the onco-biome and the tumor tissue. The direct immunomodulatory effects of the microbiome will be discussed in the next chapter.

Intestinal bacteria expressing beta galactosidases (gus and BC genes [117–119]) can deconjugate conjugated estrogens. The gus gene is widespread among bacteria, while changes in BC include *Bacteroidetes* and *Firmicutes* [119]. *Collin-sella*, *Edwardsiella*, *Alistipes*, *Bacteroides*, *Bifidobacterium*, *Citrobacter*, *Clostridium*, *Dermabacter*, *Escherichia*, *Faecalibacterium*, *Lactobacillus*, *Marvinbryantia*, *Propionibacterium*, *Roseburia*, and *Tannerella* were shown to express β -glucuronidases [120]. Goedert and colleagues provided strong evidence for the involvement of *Clostridiales* in estrogen reactivation in breast cancer patients [73, 121, 122]. The onco-biome has increased capacity to reactivate estrogens [21, 50, 73, 74, 83, 121–124] enabling their reuptake and supporting the growth of estrogen-dependent, estrogen receptor-positive (ER+) breast tumors. Of note, the capacity for estrogen reactivation was identified by pathway analysis in the breast and nipple aspirate microbiomes [57].

Bioactive metabolites, synthesized by the microbiome or the onco-biome, can act in a similar fashion to hormones and can link up the microbiome and the distantly located cancer cells [2–4, 125]. As the gut microbiome is the biggest in the body in terms of the number of bacteria, its metabolic capacity is considerable. The biosynthetic capacity of the onco-biome is suppressed compared to the eubiome [126, 127]. Multiple bioactive bacterial metabolites were identified that can modulate the behavior of breast cancer cells (Table 3). The importance of changes to the metabolome in breast cancer is further highlighted by the large number of metabolomic studies that point towards the role of the metabolome in breast cancer incidence and evolution [128–132]. The bioactive bacterial metabolites are very chemically diverse. We will briefly highlight the most important bacterial metabolites that have cytostatic features. A set of bacterial toxins contributes to the oncogenic property of the onco-biome (Table 4) similar to other neoplasias [133–135].

Lithocholic acid (LCA) is a secondary bile acid derived from primary bile acids. Mostly *Clostridia* in the large intestines are responsible for the production of LCA and secondary bile acids in general [82]; however, other taxons are also involved [191]. The enzymes involved in secondary bile acid production are assembled in the bile acid inducible (bai) operon in bacteria [191]. The production of LCA from its precursors involves the deconjugation of primary bile acids and the oxidation, epimerization, and dehydroxylation of the gonane core [2, 4, 167, 191, 192]. Secondary bile acids, such

as LCA, have pleiotropic roles in the microbiome, including regulation of the microbiome composition [193–200], facilitation of bacterial translocation into tissues [201], and quorum sensing [202, 203].

The bile acids in the breast are of the gut origin [204, 205]. Total bile acid levels in the serum of healthy individuals are lower than 5 μ M. LCA serum reference concentrations are low (30–50 nM). However, tissue levels in the breast may be substantially higher [78, 206]. In breast cancer, both the hepatic synthesis of primary bile acids and the bacterial conversion to secondary bile acids in the large intestine are suppressed, and this suppression is the most dominant in in situ carcinoma and stage I patients [78, 82]. In good agreement with this concept, serum LCA levels negatively correlate with the Ki67 labeling index in breast cancer [207]. The composition of the serum bile acid pool in patients with benign breast disease is different from breast cancer patients; breast cancer patients had higher serum chenodeoxycholic acid levels and lower dihydroxytauro-conjugated bile acids (Tdi-1) and sulfated dihydroxyglyco-conjugated bile acids (Gdi-S-1) [208]. Another secondary bile acid deoxycholic acid (DCA) may act as a procarcinogenic agent [209, 210] and may be responsible for the procarcinogenic character of secondary bile acids [211].

A multitude of receptors is involved in bile acid signaling, including *Takeda* G protein-coupled receptor 5 (TGR5) and farnesoid X receptor (FXR), which are important for the current discussion. One study [212] suggested the use of bile acid-tamoxifen conjugates for breast cancer therapy.

Multiple amino acid catabolic products derived from lysine and tryptophan have cytostatic properties in breast cancer. Indole derivatives are made from tryptophan, while lysine decarboxylation yields cadaverine.

The microbiome accounts for 4–6% of tryptophan catabolism to yield indole derivatives [213], of which indolepropionic acid (IPA) and indoxyl sulfate (IS) have cytostatic properties in breast cancer [81, 175]. The serum reference concentration of IPA is submicromolar [176, 214, 215], while IS concentrations are low micromolar [216]. The bacterial enzyme responsible for IPA and IS biosynthesis, called tryptophanase (TnaA), can be found in the tryptophanase operon [176]. Tryptophanase expression is widespread among bacteria [217, 218]. IPA and IS, similar to other indole derivatives, can activate the aryl hydrocarbon receptor (AHR) and bind to the pregnane-X receptor (PXR) receptor [219–221]. Indole derivatives have a strong immunostimulatory effect [222–224]; IPA and IS can induce antitumor immunity in breast cancer [81, 175] and modulate the composition of the microbiome [219, 225–227]. Evidence from human studies supports the role of tryptophan and indole metabolism in breast cancer. Elevated extracellular tryptophan levels decrease survival in breast cancer (Table S8 [228]). Ki67 positivity negatively correlates with

Table 3 Bioactive microbial metabolites in breast cancer

Metabolite group	Made from	Producing bacteria	Ref	Relevant enzyme(s)	Ref	Receptor	Ref	Effect	Ref
Reactivated estrogens	Conjugated estrogens	<i>Firmicutes</i> <i>Collinsella</i> <i>Edwardsiella</i> <i>Alistipes</i> <i>Bacteroides</i> <i>Bifidobacterium</i> <i>Citrobacter</i> <i>Clostridium</i> <i>Dermabacter</i> <i>Escherichia</i> <i>Faecalibacterium</i> <i>Lactobacillus</i> <i>Marvinbryantia</i> <i>Propionibacterium</i> <i>Roseburia</i> <i>Tannerella</i>	[73, 117–119, 121, 122]	β -glucuronidase (gus/BC)	[117–119]	ER α ER β mER (mER α , mER β , GPER, GPRC6, ER-X, G $_q$ -mER)	[136, 137]	OXPPOS, tamoxifen resistance, metastasis, aggressivity, hormone-induced apoptosis, EMT, proliferation, metastasis	[138–146]
Short-chain fatty acids	Non-digestible carbohydrates, branched	<i>Akkermansia muciniphila</i>	[23, 147–149]	Thioesterases, phosphate acetyltransferase, acetate kinase, phosphate butyryltransferase, butyrate kinase, lactate dehydrogenase	[150]	FFAR HDAC AHR	[151–153]	OXPPOS (direct energy substrates), apoptosis, HDAC inhibition, macrophage antimicrobial activity	[154–158]
Acetate	Chain amino acids	<i>Ruminococcus obeum</i> <i>Roseburia inulinivorans</i> <i>Bacteroidetes</i> <i>Negativicutes</i> sp. <i>Faecalibacterium</i> <i>Prausnitzii</i> <i>Eubacterium rectale</i> <i>Roseburia faecis</i> <i>Eubacterium hallii</i> SS2/1 <i>Odoribacter</i> <i>Anaeotruncus</i>							
Butyrate									
Formate									
Lactate									
Propionate									
Pyruvate									

Table 3 (continued)

Metabolite group	Made from	Producing bacteria	Relevant enzyme(s)	Receptor	Effect
		Ref	Ref	Ref	Ref
Secondary bile acids	CDCA CA	<i>Clostridium</i> <i>Enterococcus</i>	Bile salt hydrolases (BSH), 7 α / β	TGR5 FXR	Apoptosis, proliferation, VEGF production, OXPPOS, anti-tumor immunity, EMT, fatty acid biosynthesis, movement, metastasis formation, increased oxidative and nitrosative stress
LCA	7-keto-lithocholic acid	<i>Bifidobacterium</i> <i>Lactobacillus</i> <i>Streptococcus</i> <i>Eubacterium</i> <i>Listeria</i> <i>Bacteroides</i> <i>Methanobrevibacter</i> <i>Methanosphaera</i> <i>Escherichia</i> <i>Ruminococcus</i>	-hydroxysteroid, dehydroxylase (batH)	SHP	
DCA		<i>Shigella flexneri</i> <i>Shigella sonnei</i> <i>Escherichia coli</i> <i>Streptococci</i>		TAAR1, 2, 3, 5, 8, 9	OXPPOS, CSC, movement, invasion, EMT, metastasis formation
UDCA		<i>Providencia rettgeri</i> <i>Alisipes shahii</i> <i>Bacteroides xylanivorans</i> <i>Clostridium</i> <i>Lactobacillus reuteri</i>		AHR PXR	OXPPOS, CSC, movement and proliferation, invasion, EMT, metastasis formation, antitumor immunity
Biologically active amines	L-lysine	<i>Shigella flexneri</i> <i>Shigella sonnei</i> <i>Escherichia coli</i> <i>Streptococci</i>	Lysine decarboxylase (LdcC, CadA)		
Cadaverine					
Indole derivatives	Tryptophan		TnaA		
Indoxyl sulfate			SULT1, Cyp2e1		
Indolepropionic acid					

Abbreviations: CA, cholic acid; CDCA, chenodeoxycholic acid; CSC, cancer stem cell; EMT, epithelial-to-mesenchymal transition; ER, estrogen receptor; FFAR, free fatty acid receptor; FXR, farnesyl X receptor; HDAC, histone deacetylase; LPA, lysophosphatidic acid; LPS, lysophospholipids; OXPPOS, oxidative phosphorylation; TAAR, trace amine-related receptor; TGR5/GPBARI, G protein-coupled bile acid receptor 1; VEGF, vascular endothelial growth factor

Table 4 Structural and secreted bacterial toxins supporting breast cancer

Metabolite group	Made from	Producing bacteria	Relevant enzyme(s)	Receptor	Effect
		Ref	Ref	Ref	Ref
LPS	Lipid A + core oligosaccharide + O-specific polysaccharide	<i>Escherichia coli</i> <i>Salmonella enterica</i> <i>Vibrio cholera</i> <i>Pseudomonas</i> <i>Pantoea</i>	Lpx [177]	[178, 179] TLR2 TLR4	Apoptosis, migration and metastases, EMT and β -catenin signaling, invasiveness [181–183]
Lysophospholipids (LPS) Lysophosphatidic acid (LPA)	Phospholipid	<i>Vibrio cholerae</i> <i>Helicobacter pylori</i> <i>Yersinia pseudotuberculosis</i>	Phospholipase A2 Exogenous lipase [184]	LPAR1-5 [185, 186]	Proliferation, migration, metastasis, stress fiber and focal adhesion formation [187–189]
Colibactin	Precolibactin	<i>Escherichia coli</i> <i>Klebsiella pneumoniae</i> <i>Enterobacter aerogenes</i> <i>Citrobacter koseri</i>	ClbA-S [190]	Unknown [190]	Unknown

3-indoxyl sulfate levels ([207] Additional file 9, Table S8 line 130), and 3-indoxyl sulfate levels are downregulated in both estrogen receptor–positive and negative cases ([207] Additional file 3, Table S3 line 44). TnaA DNA is downregulated in the breast cancer microbiome, and the most drastic changes were observed in in situ and stage I cases [81].

In the human body, cadaverine can be of bacterial, human, or nutritional origin. Nevertheless, bacterial cadaverine production seems to dominate [79]. In bacteria, the LdcC and CadA genes are responsible for cadaverine biosynthesis [172, 229], while diamino-oxidase eliminates cadaverine [230]. The capacity for cadaverine biosynthesis was identified in a number of bacteria [231–233]. Human serum reference concentration of cadaverine is submicromolar (100–800 nM) [234, 235]. Cadaverine can activate trace amine-associated receptors (TAAR1, 2, 3, 5, 8, 9), and these receptors are associated with breast cancer [79, 174]. Fecal TnaA protein content was reduced in E-cadherin-negative breast cancer cases compared to E-cadherin-positive cases [80].

Short-chain fatty acids (SCFAs), such as formate, acetate, propionate, butyrate, and lactate, are generated by a large set of bacterial species from non-digestible carbohydrates and a minor fraction from amino acids [236]. SCFAs are formed at multiple points in bacterial metabolism and are then released into the environment. Therefore, a wide circle of bacteria can synthesize SCFAs. The reference concentration of SCFAs in the human serum is in the range of 10–100 μ M [237–239] and may reach up to 1 mM locally

[240]. The receptors for SCFAs are the free fatty acid receptors (FFARs) and AHR [151].

Oncobiosis-related changes to bacterial metabolite production support oncogenesis and not tumor initiation through multi-faceted effects. In certain cases, as for SCFAs, effects are context-dependent; SCFAs can have positive (e.g., [241]) or negative (e.g., [242]) effects in breast cancer. Many studies used metabolites in superphysiological concentrations that may render the interpretation of these studies difficult [243–246]. In superphysiological concentrations, metabolites can induce cell death [171, 244–247] and other features (e.g., in superphysiological concentrations, LCA blocked fatty acid biosynthesis [171] or induced cell death and the expression of multidrug resistance proteins [247]) that is usually mediated by secondary receptors, such as FXR in the case of LCA [247]. The metabolites assessed in the context of breast cancer were ineffective on untransformed primary human fibroblasts at their reference concentration, suggesting selectivity towards transformed cells [78, 79, 81, 97, 175].

Metabolites elicit effects by reducing oxidative and nitrosative stress through induction of NRF2 expression and its downstream effector genes and suppressing inducible nitric oxide synthase (iNOS). These effects may also involve the catechol-quinone metabolites of estrone and estradiol [81, 97, 175, 248]. Furthermore, the oncobiome contributes to the induction of Warburg metabolism in tumor cells [78, 79, 81, 97, 175]. These basic processes support epithelial-to-mesenchymal transition [78, 79, 81, 249], migration and

invasion [79, 81], increased aldehyde dehydrogenase-1 (ALDH1)-positive cancer stem cells [79, 81], and suppression of tumor immunity [22, 24, 78, 81, 175, 250, 251]. These processes together support metastasis formation [24, 78, 79, 250, 251] and disease recurrence [29]. In addition, most SCFAs can act as energy sources in cells [233] and may inhibit histone deacetylases to modulate epigenetics [152, 154–157, 241, 252–257]. LCA supplementation can reduce VEGF production by the implanted breast cancer cell in an animal model of breast cancer [78]. Furthermore, the oncobiome correlates with omega-3 polyunsaturated fatty acid homeostasis [85].

Our current understanding indicates that these metabolites only represent the tip of the iceberg. Multiple studies

[75, 87, 89] identified imputed pathways that were differentially regulated in the oncobiome and eubiome in breast cancer patients (Table 5). In addition to the metabolic changes, a large set of transport systems are dysregulated in bacteria [75]. These findings highlight the widespread effects of bacterial bioactive metabolite production.

As mentioned earlier, the suppression of the biosynthetic capacity of the microbiome is most pronounced in the early stages of the disease [79, 81, 97]. Nevertheless, studies on the expression of receptors for the metabolites suggest that receptors on the surface of tumor cells are downregulated as tumor stage or grade increases [81, 97]. The receptors for microbiome-derived metabolites and the components of the downstream signaling pathways in the tumor correlate

Table 5 Imputed metabolic pathways dysregulated in the gut oncobiome of breast cancer patients

Induced in BC patients	Decreased in BC patients	Ref
Premenopausal patients	Premenopausal patients	[75]
Beta oxidation	Uridine monophosphate biosynthesis	
Pyridoxal biosynthesis	Reductive pentose phosphate cycle (ribulose5P → glyceraldehyde3P)	
Pentose phosphate pathway (oxidative)	Pyruvate oxidation to acetyl-CoA	
Heparane sulfate degradation	Phosphatidylethanolamine biosynthesis	
Entner-Duodoroff pathway	Inosine monophosphate biosynthesis	
	Glycolysis	
	GABA biosynthesis	
	Formaldehyde assimilation, serine pathway	
	F-type ATPase	
	Dicarboxylate pathway	
	Pantothenate biosynthesis	
	C5 isoprenoid biosynthesis, non-mevalonate pathway	
	CI-unit interconversion	
Postmenopausal patients		[75]
Ubiquinone biosynthesis		
Jasmonic acid biosynthesis		
Beta oxidation		
LPS biosynthesis		
Glyoxylate cycle		
Meta cleavage pathway of aromatic compounds		[87]
Aromatic biogenic amine degradation		
Androstenedione degradation		
LPS biosynthesis	Glycolysis/gluconeogenesis	[89]
Ubiquinone and other terpenoid-quinone biosynthesis	Glycerophospholipid metabolism	
Folate biosynthesis		
Aminobenzoate degradation		
Biotin metabolism		
Glutathione metabolism		
Penicillin and cephalosporin biosynthesis		
D-Arginine and D-ornithine metabolism		
N-glycan biosynthesis		
Isoquinoline alkaloid biosynthesis		
Styrene degradation		
TCA cycle		
Geraniol degradation		
Indole alkaloid biosynthesis		

BC, breast cancer; CoA, coenzyme A; GABA, gamma-aminobutyric acid; LPS, lipopolysaccharide; TCA, tricarboxylic acid cycle

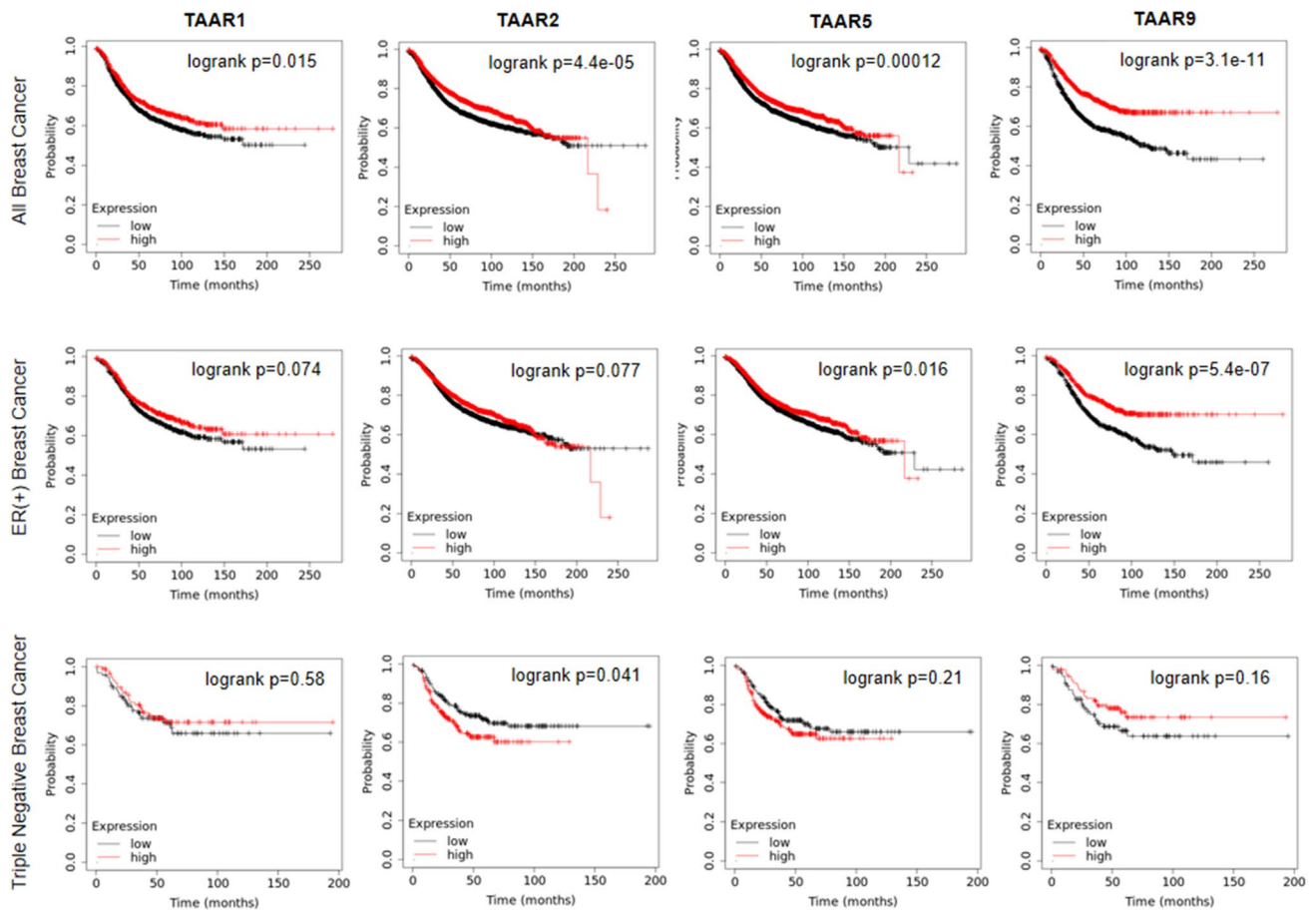


Fig. 2 High expression of a subset of TAAR receptors prolongs relapse-free survival in breast cancer patients that is abrogated in TNBC cases. Survival curves were obtained from the [kmplot.com](https://www.kmplot.com) site [258] on the 7th of October 2021

with the receptor status, grade, and stage. The intratumoral expression of AHR, PXR, and TGR5 decreases in TNBC cases compared to ER + cases [81, 97]. These findings were mirrored in relapse-free survival rates, where high expression of the receptors and their downstream signaling components provided better survival for patients that was abrogated in TNBC cases [81, 97]. In Figs. 2 and 3, we show that a subset of TAAR receptors and FFAR1 receptors have similar properties. Similarly, in LCA-elicited downstream signaling events, PXR and AHR receptor expression decreased as a function of stage, grade, or high mitotic rate [81, 97].

The impact of changes in the urinary microbiome is unexplored. However, recently, An and colleagues showed that bacterial extracellular vesicles can be isolated from the urine of healthy subjects and breast cancer patients and these extracellular vesicles can affect breast cancer cells differently [90].

3.3 Antitumor immune responses

In general, the diverse status of the microbiome supports normal immune responses that are crucial for antitumor

immunity [259–261]. Both the breast and the gut oncobiome have altered interactions with the immune system that we will review here. Whether changes to the bacterial community lead to changes to the immune system or the immune system causes changes to the microbiome remains an open question. Furthermore, myeloid and lymphoid infiltrations in tumors have differential effects; lymphoid infiltration is generally considered to have antitumor effects, while neutrophils are considered proneoplastic [262, 263]. We will discuss the microbiome-mediated changes to the immune system separately for the breast microbiome and the gut microbiome.

Before going into details, we would like to briefly introduce two bacterial immunogenic toxins, which are classified as pathogen-associated molecular patterns (PAMP). First, lipopolysaccharides (LPS) (Table 4), lipoglycans, or endotoxins are constituents of the outer membrane of Gram negative bacteria [177]. Toll-like receptor 2 and 4 respond to LPS stimulation [177, 180]. Second, lysophosphatids (Table 4) are generated in reactions related to bacterial membrane homeostasis [184, 264]. Cells of the host organism can also generate lysophosphatids. Gram negative bacteria

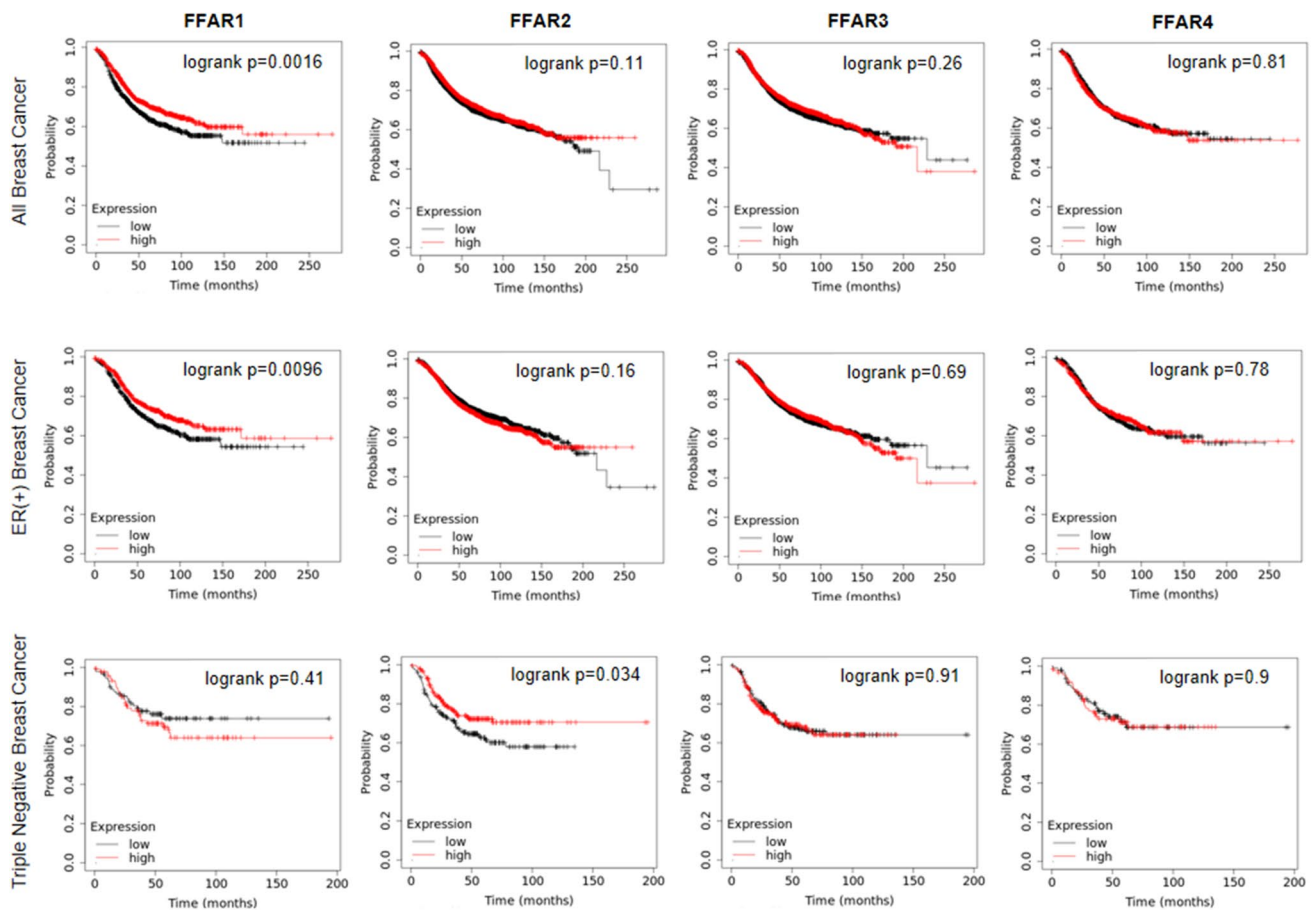


Fig. 3 High expression of FFAR1 receptors prolongs relapse-free survival in breast cancer patients that is abrogated in TNBC cases. Survival curves were obtained from the kmplot.com site [258] on the 7th of October 2021

tend to generate lysophosphatids [184, 264]. Endogenous phospholipase A2 or other exogenous lipases can generate lysophosphatids [184]. Lysophosphatids exert their effects through lysophosphatidic acid receptors (LPAR1-6) [185].

3.3.1 The breast's inherent microbiome and immune responses

The inherent microbiome of the breast and the tumor is enriched in Gram negative bacteria [67], while lipoteichoic acid, specific for Gram positive bacteria, is absent in tumors [67]. These culturable bacteria are from *Proteobacteria*, *Firmicutes*, and *Actinobacteria* [67]. Alongside these findings, LPS was detected in tumor samples [67]. Bacterial LPS and 16S rRNA were demonstrated in CD45+/CD68- cells of a highly inflamed breast tumor, indicating that the colonizing bacteria tune and activate the immune system [67]. In the nipple fluid aspirate of breast cancer patients, the genes for LPS and lysophosphatid biosynthesis were upregulated in an imputed pathway analysis [57]. Similarly, imputed pathway analysis genes related to Th17 cell differentiation were

enriched in the breast microbiome of breast cancer patients [62]. Further underlining these observations, bacterial peptidoglycan rendered breast cancer cells more invasive through activation of TLR2 receptors [261]. High intratumoral (anti-bacterial) inflammation can be boosted or sustained by viral infection [64, 91, 92]. In fact, human papillomavirus infection induces Stat3-activation and IL-17 expression in breast cancer patients [92]. Van der Merwe and colleagues [265] identified *Fusobacterium nucleatum* as a major species in the breast microbiome that overgrows in breast cancer patients, exerts an immunosuppressive phenotype, and activates the TLR4 receptor leading to immunosuppression.

Nevertheless, two studies [60, 66] refuted these observations. These studies found an association between microbiome components and inflammatory signaling. Namely, *Methylibium* and *Enhydrobacter* positively covaried with TLR signaling (*TLR3*, *TLR4*, *IRAK1*) in healthy control networks [60] and *Streptococcus* positively associated with *CD6*, *LAG3*, *SH2D1A*, and *TIGIT* expression and with T cell abundance in healthy control tissue [66]. However, in the tumor tissue, these associations [60] were lost, and the

expression of antibacterial response genes (TLR2, TLR5, TLR9, NOD1, NOD2, CARD6, CARD9, TRAF6, borderline significant NFκB, BPI, IL-12A, MPO, and PRNT3) was lost [66]. Furthermore, in tumor tissue, *Methylobacterium* showed significant negative correlations with *ICOS* and *TBX21* expression and with T cell abundance [66]. These data [60, 66] contradict the data presented by other studies [57, 62, 67, 92, 261], and this discrepancy has not been explained yet.

3.3.2 The gut microbiome and immune responses

Immune responses likely play a role in the oncobiome transformation of the gut microbiome, as multiple species, such as *Ruminococcus* and *Alistipes*, were opsonized in the stool of breast cancer patients [83]. On the other hand, the gut microbiome plays a pivotal role in fine-tuning the host's immune system. In a large-cohort fecal microbiome study, multiple taxa immune-related functions were strongly associated with breast cancer [74]. In murine models, *Lactobacillus acidophilus* [39] or *Helicobacter hepaticus* [266] were associated with immune function in breast cancer. Oral gavage of *Helicobacter hepaticus* promotes mammary tumorigenesis that is dependent on the recruitment of neutrophils to the tumor; depletion of neutrophils using a monoclonal antibody abolished the promoter effect of *Helicobacter hepaticus* [266]. Oral treatment of mice with *Lactobacillus acidophilus* improved the immune response against the experimental tumor, reduced tumor growth, and tuned the immune response towards a Th1-type response [39]. Dysbiosis in the gut is associated with enhanced macrophage infiltration (CD11b+ cells) to the breast tissue, of which the majority were M2-polarized (tolerogenic) macrophages [24]. Dysbiosis enhanced the mammary content of GM-CSF, IL23, IL22, CXCL1, and CCL2 in pretumor breast tissue that was further exacerbated in mice bearing breast tumors [24]. Mast cells also play a role in the oncobiome-induced immune effects [22].

Multiple gut-derived bacterial metabolites possess immunomodulatory roles in breast tumors. Lithocholic acid, indolepropionic acid, and indoxyl sulfate are produced in the intestines and can regulate tumor immune response against cancer cells in experimental models of breast cancer [78, 81, 175]. Butyrate may have immunomodulatory roles at multiple levels that were not directly assessed in breast cancer [267].

4 The role of oncobiosis in metastasis formation, survival, and recurrence in breast cancer

Reports unanimously show that dysbiosis supports invasion and metastasis formation [24, 54, 78, 79, 250, 251]. However, reports concerning the association of species with node

positivity or metastasis formation are divergent. In the breast microbiome, *Methylobacterium* decreased in cases with lymphovascular invasion [54]. In another study [60], node positivity was associated with *Acinetobacter* and *Bacteroides* and negatively associated with *Achromobacter*. Lymphovascular invasion was positively associated with *Lactobacillus* and negatively associated with *Alkanindiges* abundances. Reduced *Oblitimonas* abundance was associated with both lymphovascular invasion and node-positive status. *Brevundimonas* abundance increased in patients developing distant metastases [250].

What are the modalities through which oncobiosis can support metastasis formation? The oncobiome-elicited anti-metastatic and anti-recurrence effects on breast cancer are multi-pronged (Fig. 4). The breast cancer microbiome is associated with extracellular matrix degradation (e.g., dermatan sulfate degradation [67], suppression of peptidoglycan biosynthesis [57], and proteoglycans homeostasis [62]) that can support cellular movement within the tissue. The physical presence of bacteria can promote breast cancer cell invasiveness by activating toll-like receptor 2 on cancer cells via bacterial peptidoglycan [261]. The oncobiosis of the GI tract can also support cellular movement. For example, cadaverine, a cytostatic bacterial metabolite of the GI tract, can suppress breast cancer cell movement in in vitro assays and suppress matrix metalloproteinase-9 expression [79]. Furthermore, fecal TnaA protein content, responsible for bacterial cadaverine biosynthesis, is reduced in E-cadherin negative breast cancer cases compared to E-cadherin positive cases [80].

Improved tissular displacement of cancer cells accompanies the process of epithelial-to-mesenchymal transition (EMT). Intratumoral *Listeria fleischmannii* is associated with EMT [68]. Cytostatic bacterial metabolites (lithocholic acid, cadaverine, indoxyl sulfate, indolepropionic

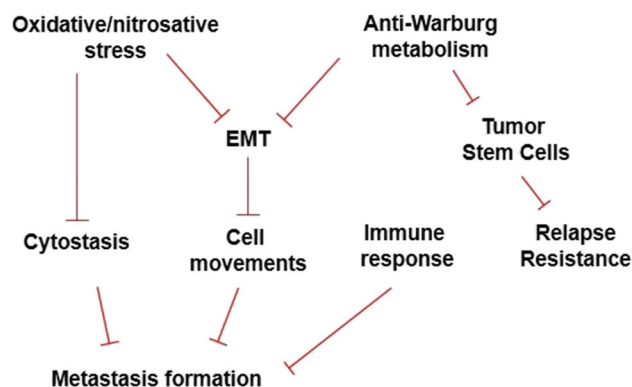


Fig. 4 An overview of the processes through which the healthy eubioime suppresses metastasis formation and supports recurrence in breast cancer. These processes are lost in breast cancer-associated oncobiosis

acid), which are lost in breast cancer, can suppress EMT [78, 79, 81, 175]. These metabolites can improve the expression of E-cadherin and ZO-1 and mesenchymal markers (Vim, Fgfbp1, Tgfb3, MMP9, Snai1, β -catenin) [78, 79, 81, 249]. Altogether, these processes support migration and invasion [79, 81].

A very important contribution from Buchta Rosean [24] provided evidence that preexisting dysbiosis of the GI tract, induced by antibiotic treatment, supports tumor growth and metastasis formation in a murine model of breast cancer. Gut dysbiosis/oncobiome induces an inflammatory response in the breast tumor, meloid cell infiltration to tumors, tumor fibrosis, and tumor dissemination. These proneoplastic, prometastatic traits can be induced in mice by transfer of fecal content from tumor-bearing mice.

In addition to cellular movement and EMT regulation, bacterial metabolites from the GI tract, such as lithocholic acid [78, 97] cadaverine [79], indolepropionic acid [81], and indoxyl sulfate [175], can suppress cellular proliferation. Furthermore, lithocholic acid reduces VEGF expression in experimental tumors [78]. These processes decrease the likelihood of tumor growth and blood or lymph vessel infiltration. The synthesis of these bioactive metabolites is suppressed in breast cancer patients [78, 79, 81]. An interesting observation from Absil and colleagues suggests that FXR, a bile acid receptor, plays a major role in setting the osteotropism of breast cancer cells [268].

The microbiome apparently has an impact on the neutrophil-to-lymphocyte ratio, which is a prognostic factor in breast cancer patients [263, 269]. Higher proportions of lymphocytes support antitumor immunity and reduce metastatic behavior, while higher neutrophil ratios support cancer progression and metastasis formation. As noted above, orally administered *Helicobacter hepaticus* promotes mammary tumorigenesis through neutrophil recruitment to tumors [266]. In contrast, among the bacterial metabolites, lithocholic acid [78] and indolepropionic acid [81] can induce higher proportions of tumor-infiltrating lymphocytes.

The composition of the oncobiome changes as a function of disease stage [60, 78, 79, 81] in breast cancer and, hence, is associated with survival. Antibiotic overdosing, which induces oncobiome and supports the development of breast cancer, can increase the frequency of disease recurrence [29]. Components of the intratumoral and tisular microbiome correlate with patient survival [70, 72]. Based on the assessment of over 1000 archived breast cancer tissue samples, 46 bacteria were identified as risk factors (including *Leptospira*, *Desulfotalea*, *Archangium*, *Dicipivirus*, *Halosimplex*, *SpoIvirus*, *Candidatus_Amoebophilus*, *Roseibium*, and *Arcticibacter*), while 48 bacteria were identified as favorable factors (including *Gordonia*, *Planktothricoides*, *Lachnoclostridium*, *Bafnivirus*, *Actinomadura*, and *Methanothermus*) [72]. Mao and colleagues [72] identified

bacterial patterns in breast cancer tissue that strongly correlate with prognosis; poor and good prognosis patients could be separated based on these bacterial patterns (AUC > 0.8). Terrisse et al. [86] demonstrated that stool/fecal transfer of the human microbiome into tumor-bearing mice transformed the properties of the mouse tumors to the human counterpart (e.g., rapidity of progression).

Oncobiome is also associated with disease recurrence. Kim et al. reported that when comparing patients with high and low risk of regional recurrence of breast cancer, bacterial pentose and glucuronate interconversions and *Enterococcus* were the main discriminating factors [95]. In support of these observations, antibiotic overdosing can increase the likelihood of disease recurrence [29].

Although little is known about the processes supporting disease recurrence, aldehyde dehydrogenase-1 (ALDH1) positive cancer stem cells are likely to have a supportive role. Bacterial metabolites (cadaverine and indolepropionic acid) produced by the healthy gut eubiome can reduce the proportions of ALDH1 + cancer stem cells in cultured cells [79, 81], leading to reduced recurrence and therapy resistance (Fig. 4). In breast cancer patients, the production of these metabolites is suppressed, supporting the expansion of ALDH1 + cancer stem cells [79, 81]. As noted earlier, widespread metabolic rearrangements were identified in the cancer tissue oncobiome [55–57, 59, 62, 67] and the gut oncobiome that encompass elements of Warburg metabolism [75, 78, 79, 81, 87, 89, 175]. Warburg-type metabolism may be a molecular mechanism through which oncobiome supports ALDH1 + cancer stem cell formation.

5 The role of the breast cancer oncobiome in chemotherapy

Neoadjuvant is a chemotherapeutic procedure aimed at shrinking tumor size to enable surgical excision. The microbiome metabolizes chemotherapeutic drugs, including those used in the (neoadjuvant) chemotherapy of breast cancer [270]. Hence, the microbiome can fundamentally change the pharmacokinetics and pharmacodynamics of these drugs (reviewed in [3, 4, 270, 271]). Not surprisingly, antibiotics modulate the pharmacokinetic and pharmacodynamic properties of chemotherapeutic drugs and the therapeutic outcome [272]. *Pseudomonas aeruginosa*-conditioned medium affected breast cancer cell proliferation and doxorubicin-induced cell death, highlighting the role of secreted bacterial metabolites and toxins [250], or possibly bacterial extracellular vesicles [90].

Most chemotherapy agents have antimicrobial effects and, thus, affect the microbiome [4]. In line with that

concept, neoadjuvation changes the composition of the microbiome [86, 88, 250]. In terms of diversity, the reports show differences between compartments. Chiba et al. [250] reported decreased alpha diversity in breast microbiome in patients undergoing neoadjuvation compared to those undergoing surgery without neoadjuvation. With regard to the gut microbiome, Terrisse et al. [86] reported increases in alpha diversity between stool samples from the same patient undergoing neoadjuvant chemotherapy and after the completion of neoadjuvant chemotherapy. Beta diversity values were able to separate patients according to tumor size, grade, auxiliary node involvement, and TNM stage [86]. Wu and colleagues confirmed increases in alpha diversity of the gut microbiome upon neoadjuvation [88].

Chiba et al. [250] showed that *Pseudomonas* species increased, while *Prevotella* decreased in tumors undergoing neoadjuvation in the breast microbiome. Wu and colleagues [88] reported changes to *Bacteroidetes* (g_*Alistipes*), *Firmicutes* (g_*Clostridium*, g_*Eubacterium*, g_*Bilophyla*), and *Proteobacteria* (g_*Haemophylus*) in the gut microbiome. Terrisse et al. [86] reported a large set of biochemical pathways that were differentially regulated between the pre- and postneoadjuvant samples in the gut microbiome. Most of these pathways were involved in amino acid and nitrogen metabolism [86].

6 Conclusions

The involvement of the microbiome in breast cancer is compelling. From a clinical perspective, it is important to understand that oncobiome has to be preexisting [24]. In other words, dysbiosis is a factor that supports carcinogenesis but is unlikely to be the cause of the disease. The interactions between the different pools of the microbiome and breast cancer cells are multi-pronged. The microbiome plays a pivotal role in preventing the metastatic spread of breast cancer [24, 78, 79, 81, 175]. Furthermore, the oncobiome interacts with chemotherapy [86, 88, 250] and has an impact on disease recurrence [250]. Altogether, these data point out a possible role of managing the microbiome to provide novel leverage on breast cancer. These strategic considerations encompass the use of prebiotics [36], probiotics [37–45], diverse nutrition [46–49], and the careful use antibiotics to reduce the risk for breast cancer incidence and recurrence [22–33].

Microbiome changes with the stage, grade, or subtype of breast cancer. Hence, these stratifications should be assessed and patients in the study should be reported with all details. A good example of such a study design can be found in the paper of Plaza-Diaz and colleagues [273]. Along the same line, protocols for identifying external

contaminations to the microbiome are very important [8, 69, 274], especially in samples with low biomass.

The microbiome possesses a large set of possible biomarkers; the different subtypes of breast cancer have different microbiomes that can be distinguished [70, 75]. Reports have identified possible markers both at the level of nucleic acids [69, 70, 72, 75] and at the protein level [81] in the breast and stool for the detection of the disease. Certain markers are quite promising (ROCs between 0.888 and 0.917). We would also like to point out a large number of review papers discussing diagnostic issues [275–279]. As mentioned earlier, microbiome biomarkers can potentially be used to assess the microbiome-chemotherapy interactions and be a useful source of data in personalized medicine. Taken together, the microbiome-breast cancer interactions have wide applicability from the clinical perspective that warrants future studies and applied discoveries.

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Declarations

Conflict of interest The authors declare no competing interests.

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