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Is the skin microbiota a modifiable risk factor for breast disease?: A systematic review

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ABSTRACT

Purpose: High prevalence, unreliable risk discrimination and poor clinical outcomes are observed in malignant and benign breast diseases (BD). The involvement of microbial communities in the development of BD has become topical, and distal influences of microbial dysregulation in the breast have been well established. Despite advances, the role of the breast skin microbiota in BD remains unclear. Interactions between the skin microbiota and the underlying mucosal immune system are complex. In homeostasis, the skin offers a physical barrier protecting underlying breast tissue from skin commensals and noxious environmental triggers. Our review aims to illuminate the role of the skin microbiota in the development of BD.

Methods: Adhering to the PRISMA protocol, a systematic review was conducted utilising the Medline and Embase search engines.

Results: Through a comprehensive search of the last ten years, twenty-two studies satisfied the inclusion criteria. *Proteobacteria*, *Firmicutes*, *Actinobacteria* and *Bacteroidetes* were identified as the most prevalent phyla of both breast tissue and skin in healthy controls and BD. High abundance of skin commensals, specifically some species of *Staphylococcus*, have been linked in breast cancer and metastases. Similarly, dysregulated microbial abundance is also seen in inflammatory and implant-associated BD. These findings raise the hypothesis that the skin microbiota plays a role in tissue homeostasis and may contribute to a range of breast pathologies. Several mechanisms of microbial transfer to underlying tissue have been proposed, including retrograde transfer through ductal systems, breakdown of the skin barrier, and migration through nipple-aspirate fluid.

Conclusion: Our review provides preliminary insights into the skin microbiota as a modifiable risk factor for BD. This raises opportunities for future studies in antimicrobials/probiotics as an adjunct to, or replacement of surgery; a diagnostic and/or prognostic tool for BD; and the possibility of conditioning the microbiota to manage BD.

Contents

Abbreviations: BD, breast disease; BC, breast cancer; CC, capsular contracture; HC, healthy control; GLM, granular lobular mastitis; BIA-ALCL, breast implant-associated anaplastic large cell lymphoma.

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1. Introduction

1.1. Significance of breast disease

Breast disease (BD) consists of cancerous (malignant) and noncancerous (benign) conditions. Breast cancer (BC) accounts for nearly one quarter of all cancers worldwide [1]. Risk discrimination remains poor, with ~70 % of BC cases occurring in women of average risk [2]. Despite significant therapeutic advances and reduction in mortality rates, BC continues to be the major cause of cancer-related deaths in women [3]. Granular lobular mastitis (GLM) is an inflammatory breast disease known to clinically mimic BC [4]. Whilst showing a high rate of resolution and remission, there has been a shift away from undesirable surgical intervention [5]. Furthermore, complications of breast implant surgery remain a significant burden, responsible for a great proportion of surgical revisions [6].

1.2. Microbial impact on disease

Microbial environments have shown to influence the expression of genes and cellular differentiation of the immune system [8]. Dysregulation of microbial homeostasis (referred to as dysbiosis), has been recently reported in BC and other BD [9]. Certain bacterial taxa are ubiquitous among studies, whilst others note the impact of more rare bacterial lineages with disease onset [9]. Distal sources influencing the breast microbiota, such as the entero-mammary pathway [10], have been well established in the literature, and growing evidence has further assessed the role of urine [11], oral [10,12,13], and vaginal [7] microbes. Despite major advances, how the breast skin microbiota contributes to breast dysbiosis and the development of BD at present remains unclear.

1.3. The skin: a symbiotic relationship

The skin is composed of an abundance of folds, invaginations and specialised niches which support a microbial ecosystem unique to its anatomical region [14]. Skin commensals, such as *Staphylococcus epidermidis,* can establish lifelong symbiotic relationships with their host. They provide benefits through aiding in nutrition, outcompeting pathogens, and educating the innate/adaptive immune system [15]. Influences of the skin microbiota extends beyond hygiene. Colonisation is driven by the ecology of the skin's surface, including: (i) the unique anatomical region, (ii) changes over a lifetime, and (iii) influences of endogenous and exogenous factors [14] (Fig. 1). Herein, the 'breast skin' is our primary focus. The anatomy of the nipple-areolar complex is unique: a multi cell-layered structure containing numerous nerve endings, sebaceous and apocrine sweat glands [16]. Skin dysbiosis has been established with breast skin conditions (psoriasis and atopic dermatitis) [14], and skin morphological changes are seen with underlying BD (erythema, dimpling, oedema and peau d'orange) [17]. Skin dysbiosis has also been linked with skin cancer through the induction of chronic self-maintaining inflammation [18,19]. However, it is still largely unknown whether skin dysbiosis has structural and/or functional influences on underlying breast tissue, and to what extent that precipitates BD development.

1.4. Objective

Our review aims to appraise the literature and illuminate the role of the breast skin microbiota in the development of BD. This raises opportunities for modification and manipulation of the skin microbiota as a conduit to personalised medicine in BD.

2. Methods

2.1. Data sources and searches

We performed a systematic review of the literature following the standard Cochrane Collaboration methods and adhering to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) recommendations [20].

A structured electronic literature search was conducted, using Medline and Embase databases. The search strategy consisted of the keywords and MeSH terms for the breast skin microbiota and breast tissue microbiota: 'skin', 'epidermis', 'tissue'. 'microbiota', 'microbiome', 'breast'. Date of publication was limited to the last 10 years. The following filters were applied: language (English) and species (human). A hand search of bibliographies was conducted to identify any additional articles. All titles and abstracts were independently reviewed by two of the authors. If there was disagreement between the reviewers, the inclusion of studies was determined by consensus. All study types: randomised control

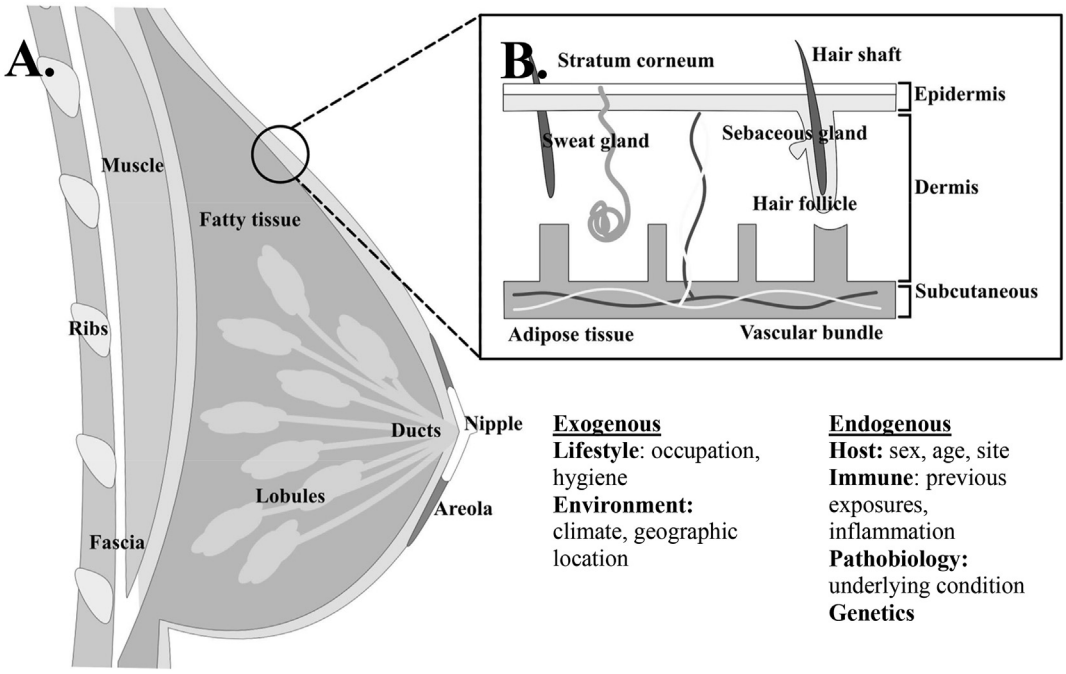

Fig. 1. Schematic of the breast and breast skin anatomy illustrating unique niches where microbes can reside, and exogenous and endogenous factors that can contribute to variation in breast microbiota over a lifetime.

trials (RCTs), case–control, cohort and case studies were eligible for inclusion; reviews were excluded.

The different study designs and the heterogeneity of the outcomes reported in the studies precluded the possibility of pooling data across the studies. Therefore, a narrative synthesis was conducted. Key study characteristics and methodological quality are described in Supplementary Tables 1 and 2.

3. Results

3.1. Literature search

The search identified 478 articles (Fig. 2). After duplicates were removed, 414 papers were screened for inclusion. 347 articles were excluded following title and abstract screen and a further 45 based on study type, excluding a total of 392. Twenty-two articles were selected for data extraction. Hand search of bibliographies yielded no additional papers. Articles appraised date from 2014 to 2020.

3.2. Key study characteristics

Developments in DNA/RNA sequencing technologies have provided the opportunity to closely monitor potential association(s) between the development of BD and the tissue's resident microbiota. Breast skin and breast tissue samples from healthy controls (HC) and BD were of interest. Variation in sequencing methodologies among the publications is shown in Supplementary Tables 1 and 2, along with patient demographics, sample size, sample sites.

3.3. Phyla of healthy and diseased breast

Collectively, all studies identified *Proteobacteria*, *Firmicutes*, *Actinobacteria* and *Bacteroidetes* as the main residents of the breast microbiota. Table 1 highlights the relative abundance of the phyla with respect to HC *versus* BD in both breast skin (Table 1A.) and breast tissue (Table 1B.).

Proteobacteria and *Firmicutes* are observed in greater abundance in comparison to other taxa across the studies appraised. Significant species diversity has been identified in *Proteobacteria* residing

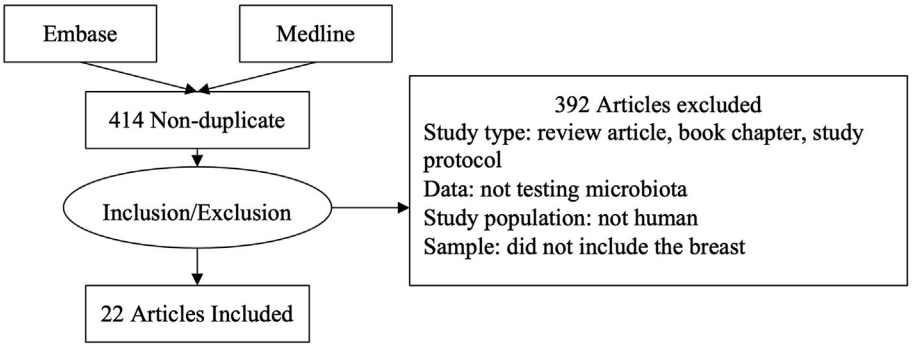

Fig. 2. Flowchart of breast skin/tissue literature search.

Table 1
Summary of relative phyla abundance across studies for breast skin (**A.**) and breast tissue (**B.**). Proteobacteria (P), Firmicutes (F), Actinobacteria (A), Bacteroidetes (B), Other (O). Studies included in this analysis that did not comment on phyla abundances were omitted from the table.

(A.)

		Phyla				
		P	F	A	B	O
Healthy Control	Bachour 2019					
	Gaitanis 2019					
	Park 2018 (Case 1)			-	-	-
	Park 2018 (Case 2)			-	-	-
Paired-Normal Tissue	Pannaraj 2017					
	Chan 2016					
Benign Tumour	Hieken 2016					
Malignant	Chan 2016					
	Hieken 2016					
Inflammatory	Park 2018 (Case 1)			-	-	-
	Park 2018 (Case 2)			-	-	-

Legend	Relative phyla abundance (%)
	0
	1-10
	11-25
	26-50
	51-75
	76-100

(B.)

		Phyla				
		P	F	A	B	O
Healthy Control	Klann 2020					
	Smith 2019					
Paired-Normal Tissue	Thyagarajan 2020					
	Smith 2019					
	Costantini 2018					
	Thompson 2017					
	Hu 2016					
	Urbaniak 2016					
	Xuan 2014					
Benign Tumour	Meng 2018					
	Heiken 2016					
	Urbaniak 2016					
Malignant	Klann 2020					
	Thyagarajan 2020					
	Smith 2019					
	Costantini 2018					
	Meng 2018					
	Thompson 2017					
	Heiken 2016					
	Urbaniak 2016					
	Xuan 2014					
Implant - ALCL	Hu 2016					

within the skin. Genealogical research has shown that pathological *Proteobacteria* found in the environment can be harboured in the skin [21], causing difficulty in delineating pathological microbes from commensal.

Similar to what is observed in the skin samples, the breast tissue demonstrates predominance of *Proteobacteria* and *Firmicutes* (Table 1B.). Reduced *Proteobacteria* abundance in BD samples is evident in studies comparing HC to BD [22–25]. Although subtle differences in Firmicutes abundance between HC and BD samples are observed, no overarching trend in predominance of these organisms can be established at the phyla level. Lack of clarity towards the prevalence of cutaneous microbes in breast tissue dysbiosis warrants closer examination of the microbiota at the genus and species level.

3.4. A closer look into dysbiosis

Dysbiosis is the result of introduced pathogenic microbes, or loss of symbiotic microbes (Fig. 3). Studies supporting the former raise questions as to whether the penetration of skin commensals to underlying tissue provides the opportunity for bacteria to become pathobiontic. *Staphylococcus*, is a common skin commensal that has evolved strategies for surviving on the skin, including the ability to be halotolerant, and utilise urea that is present in sweat as a nitrogen source [26]. *Staphylococcus*, along with *Methylobacterium*, *Enterobacter* and *Streptococcus* have also shown survivability in fatty-acid environments such as the breast [7]. These skin microbes have not only demonstrated the ability to habitat a new environment but also metabolise fatty-acids, resulting in possible deleterious changes to the microarchitecture of the tissue.

Alternatively, a notable decrease in symbiotic microbes like *Prevotella*, *Lactococcus*, and *Sphingomonas* have been associated with BD [9,22,25,27,28]. A possible explanation pertains to the interaction between the microorganisms and activation of natural killer cells to inhibit tumour growth [27]. Logically, a reduction in such microorganisms within the breast tissue would hinder any tumour-suppression and immune response. The effect of these bacteria, and several others, in the pathogenesis of BD and modulation of cellular immunity needs further investigation.

3.5. Breast cancer and the breast skin microbiota

Heiken et al., is the only study that directly compares breast skin against breast tissue in HC and BC paired samples. The authors suggest that the microbial landscape of breast tissue is distinct from that of the overlying skin tissue, exhibiting greater species richness primarily in rare or less abundant bacterial lineages [9]. The paper did not comment on whether skin dysbiosis occurred during BC, but Chan et al., concludes that there is no breast skin dysbiosis associated with BC [29]. No significant relationship has been established between skin dysbiosis and BC.

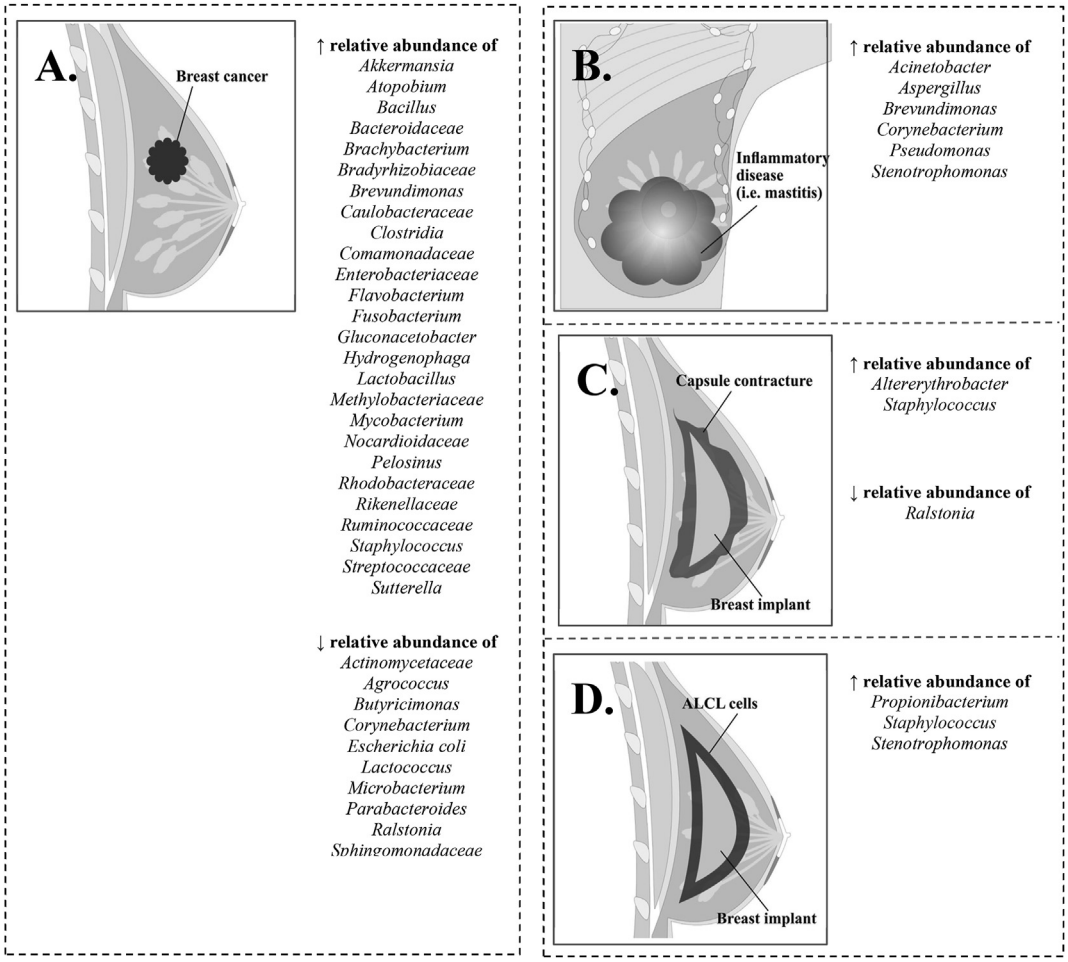

Fig. 3. Microbial shifts contrasting HC and BD tissue samples. **A**: BC compared to HC. **B**: Inflammatory BD compared to HC. **C**: CC compared to HC; and **D:** BIA-ALCL compared to HC.

A study conducted by Urbaniak et al., provides greater insight into the role of skin bacteria in BC. *Staphylococcus*, a common skin commensal, was among the most abundant genera identified in BC tissue [24,27,28] and has further been implicated in BC metastasis [30]. Further characterisation of the species within the *Staphylococcus* genus is needed to understand which are involved in the breast oncogenic process. Literature has highlighted *Staphylococcus aureus* as a common culprit for carcinogenesis. It has been shown that the incidence of primary cancers is greater following *S. aureus* bacteraemia [31], and a strong association is seen with *S. aureus* colonisation and squamous cell carcinoma [32].

Other taxa shown to have increased prevalence in BC include: *Bacillus, Bacteroidetes, Brevundimonas, Comamonadaceae, Enterobacteriaceae, and Methylobacterium* [24,25,27] (Fig. 3). Literature has found the skin microbiota to harbour these taxa [14], speculating the potential for microbial transfer from the skin to tissue. *Brevudimonas*, found in the dermis, has been reported as a clinically important pathobiont in cases of immunocompromised individuals [33]. In some instances, contaminants introduced from the operator and environment to the DNA sequencer have resulted in false positives. *Methylobacterium* has been identified as one of the common contaminants in a study conducted by Bay et al., 2020 [34].

3.6. Inflammatory breast disease and the breast skin microbiota

The role of skin microbiota can be surveyed beyond the scope of malignant disease. Three studies included in this review addressed the breast microbiota and its association with inflammatory BD disease.[4,35,36] Park et al., proposed that skin dysbiosis in atopic dermatitis (AD) was the source of breast abscess development [35]. Patients with AD exhibit significantly higher abundance of *S. aureus* in diseased skin compared to healthy skin [14]. Breakdown of the epidermal layer experienced in individuals with AD presents an opportunity for skin microbes to transfer and cause deep tissue infection.

Granular lobular mastitis is a rare, poorly understood inflammatory disease of the breast. Studies consistently report *Corynebacterium* as a dominant genus found in the taxonomic profiles of GLM patients [4,36]. *Corynebacterium* has been associated with normal skin flora as well as with acute/chronic skin and soft tissue infection [37]. *Corynebacterium kroppenstedtii*, among other lipophilic *Corynebacterium* species [38], have been implicated in the development of GLM through generation of an auto-immune response [39,40]. Other taxa seen at higher prevalence in GLM include *Pseudomonas, Brevundimonas, Stenotrophomonas, Acinetobacter*, and *Aspergillus*. The most identified species included *Pseudomonas aeruginosa* and *Pseudomonas stutzeri*. *Pseudomonas aeruginosa* can be commonly found on the skin, especially in the axillary and anogenital regions [41,42]; areas sharing similar traits to that of the nipple. These cutaneous microbes possess fatty-acid metabolising capabilities, and as discussed previously, can become pathobiontic in breast tissue [43].

3.7. Complications of breast implants and the breast skin microbiota

The role of the breast skin microbiota in the pathogenesis of breast implant complications has been discussed for breast capsular contracture (CC) [44,45], and breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) [46,47]. CC and BIA-ALCL are considered significant complications in breast augmentation and implant-based breast reconstruction surgery [6]. Previous literature primarily attributes the development of these complications to subclinical infection and bacterial biofilms following contamination of implants during surgical insertion [48].

Clear correlation between CC and the presence of *Staphylococcus epidermidis* has been established [45,49]. Notably, Bachour et al., identified the presence of *Staphylococcus* spp. on only 8% of breast capsule samples. The authors propose that bacterial transfer during implantation is highly unlikely and any resultant bacteria observed is due to contamination during removal of capsules [44]. Coagulase-negative *Staphylococci* [50], *Cutibacterium acnes* [51], and *Pseudomonas aeruginosa* [52] are also commonly found in surgical site infections, as well as in healthy human skin [53]. Transfer via surgical instruments allow the potential for opportunistic subclinical infection, and subsequent breast-implant complications.

In addition to CC, bacterial colonisation and biofilm formation has been associated with BIA-ALCL [46]. Walker et al., found *Staphylococcus* spp. to be the most commonly colonised microbe in both the BIA-ALCL and contralateral control breast [47]. Alternatively, Hu et al., observed significantly higher abundance of *Staphylococcus* spp. in non-tumour capsule specimens when compared to BIA-ALCL specimens [46]. Significantly greater proportion of *Ralstonia* spp. was present in BIA-ALCL specimens, but there is no evidence to suggest *Ralstonia* is endogenous to the skin. Uncertainty towards dysbiosis as a causative agent in the development of implant-associated disease warrants greater attention and research.

3.8. Mechanisms of microbial transfer

Mechanisms of bacterial transfer between the skin and breast are largely unknown, although various hypotheses have been proposed. Concerning breast implant surgery, iatrogenic breakdown of the skin barrier results in underlying tissue contamination by skin commensals, this was demonstrated by Rieger et al., and Carvajal et al., in the development of CC and BIA-ALCL [45]. Similarly in AD, Park et al., suggested that the high bacterial density, altered skin barrier, and immune dysregulation caused resident *S. aureus* to penetrate deep into the tissue [35]. Translocation of skin microbiota to tissue in BC and other BD characterised with intact skin is more uncertain. Retrograde transfer via the nipple and ductal system [12], altered immune responses of the skin [15] and migration through nipple aspirate fluid [25] have all been proposed as potential mechanisms at play [54].

3.9. Biases and limitations

Next-generation sequencing has allowed for rapid and accurate developments in profiling the microbiota on body surfaces. Despite advances, there are still some biases and limitations that require consideration. The microbiota is influenced by several confounding factors; both internal and external [55]. The variability seen in the microbiota among individuals presents challenges in drawing definitive conclusions, and affects the reliability of causal inference [55]. The lack of standardised methodologies (sample collection, preservation, transportation and time to analysis) continues to be a well-established limitation when comparing studies [56,57]. The effect of bias can lead to the discovery of non-existent bacterial genera, misinformed correlations between microorganisms and disease, and missed detection of true correlations. Bias may also be observed by the exclusive utilisation of 16 S rRNA gene sequencing. It has been shown in the gut microbiota that shotgun sequencing (also known as metagenomic sequencing) has more power to identify less abundant taxa, and the less abundant genera detected are biologically more meaningful [58]. Moreover, it is difficult to summarise the alpha diversity (species richness within a sample) and beta diversity (species richness between samples) due to different statistical and bioinformatics analyses being used across studies.

4. Conclusion

Investigation into the breast skin microbiota as a modifiable risk factor for BD has attained promising evidence. Given the vast number of associations between commensal breast skin microbes and BD, the breast skin microbiota seems to function as a source of pathogenicity to breast tissue.

Scope for clinical application is broad. Chlorhexidine, a preoperative skin antiseptic solution, is already being implemented in modern practices to reduce implant contamination [45]. Antimicrobials are being used for their anti-proliferative, pro-apoptotic and anti-epithelial-mesenchymal-transition (EMT) capabilities [59]. Although effective in infections, the interplay of antibiotics and the healthy microbiota makes broad application more complex. Studies have suggested that antibiotics could adversely impact cancer treatment by disrupting intestinal microbiota, altering normal tissue metabolism, and weakening the immune response [59]. Alternatively, the prospect of probiotics as a therapeutic means of introducing healthy bacteria to modulate disease is gaining prominence. Promising benefits have been seen in non-infectious skin conditions including acne, rosacea and protection against aging and damage [8]. The breast skin provides an opportunity for topical antimicrobial/probiotic treatment of BD. In addition, understanding the skin microbiota can also assist in early screening and diagnosis of BD, as demonstrated in preliminary studies using the urine microbiota [11]. Another use includes their role as a prognostic predictor, as preliminary studies suggest that microbiota characteristics can influence the response to chemotherapeutics or determine the risk of metastasis [18,30].

More evidence establishing the role of the skin microbiota is needed, including establishing a standardised protocol for characterising clinically significant microbes, understanding environmental influences, the cellular and molecular host-microbe interaction, and mechanism of transfer from skin to tissue. Greater understanding will provide significant opportunities for not only clinical management strategies as listed above, but also the potential in engineering/manipulating the human microbiota to manage disease.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.07.014.

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