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Peer reviewed by two members of Breast Cancer UK independent Science Panel

1. Summary

The human microbiome, all the microbes and their genes found in the human body, plays a key role in influencing health and the development of diseases. The role of the gut microbiome has been extensively studied in relation to breast cancer risk, showing that dysbiosis, an imbalance in bacterial composition or distribution, of the gut microbiota is linked to a higher risk of breast cancer through different mechanisms. Other microbiomes and breast cancer risk are being studied, such as the breast, breast skin and oral microbiomes; however, to date, the strongest links identified are with the gut microbiome.

2. Introduction

In the UK, breast cancer is the most common cancer [1]. Each year, around 56,000 women and 400 men are diagnosed with breast cancer, which represents 15% of all new cancer cases in the UK [1]. Many factors can influence a person's risk of developing breast cancer, including age, circulating hormones, genetics, diet, lifestyle and the environment [1,2]. Breast Cancer UK estimates that at least 30% of all breast cancers are attributable to preventable causes. Diet and lifestyle are known risk factors for breast cancer, therefore the microbiome, particularly the gut microbiome, has drawn considerable interest as an additional risk factor for breast cancer. In this review, we focus on the gut microbiome to explore the relationship between the microbiome and breast cancer, looking at the

Glossary box:

Dysbiosis: changes or imbalance in the composition or distribution of a microbiota.

Metabolites: substances made or used when the body breaks down food, drugs or chemicals, or its own tissue.

Microbiome: the microorganisms in a particular habitat of the body, and their structural elements, metabolites, interactions and the surrounding environmental conditions.

Microbiota: all the microorganisms (bacteria, archaea, fungi, algae, and protists) in a particular habitat of the body.

Normobiosis: the normal balance of microorganisms in a microbiota.

Oestrobolome: microorganisms that metabolise and regulate oestrogen, altering its bioavailability and affecting oestrogen levels in the body.

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different mechanisms through which it can impact breast cancer risk.

3. The microbiota and the microbiome

The terms “microbiome” and “microbiota” are often used interchangeably, but it is essential to distinguish them as they indicate different concepts. The human body harbours a vast and complex community of microorganisms that interact with one another and the host; this is the microbiota. It includes all the microbes (bacteria, archaea, fungi, algae, and protists) in a particular habitat of the body [3]. The microbiome refers to both the microorganisms and their “theatre of activity”, including structural elements (nucleic acids, proteins, lipids, polysaccharides), metabolites (signalling molecules, toxins, organic and inorganic molecules), and the surrounding environmental conditions (Figure 1) [3].

Glossary box (cont.):

Phyla: plural of phylum, a classification or taxonomic category for organisms, that ranks above class and below kingdom.

Symbiotic relationship: a mutually beneficial relationship between two different organisms.

The human body has trillions of microorganisms, far outnumbering the number of human cells, and each individual has a unique composition of these microorganisms [4]. The different niches or habitats for microorganisms of the human body include the gastrointestinal tract (gut), skin, mouth (oral), breast, vagina, prostate and bladder, among others (Figure 2). The microbiota of each of these organs is different and varies in quantity and diversity [5,6]. The gut microbiome is the largest and most diverse of all the human body niches, followed by the skin

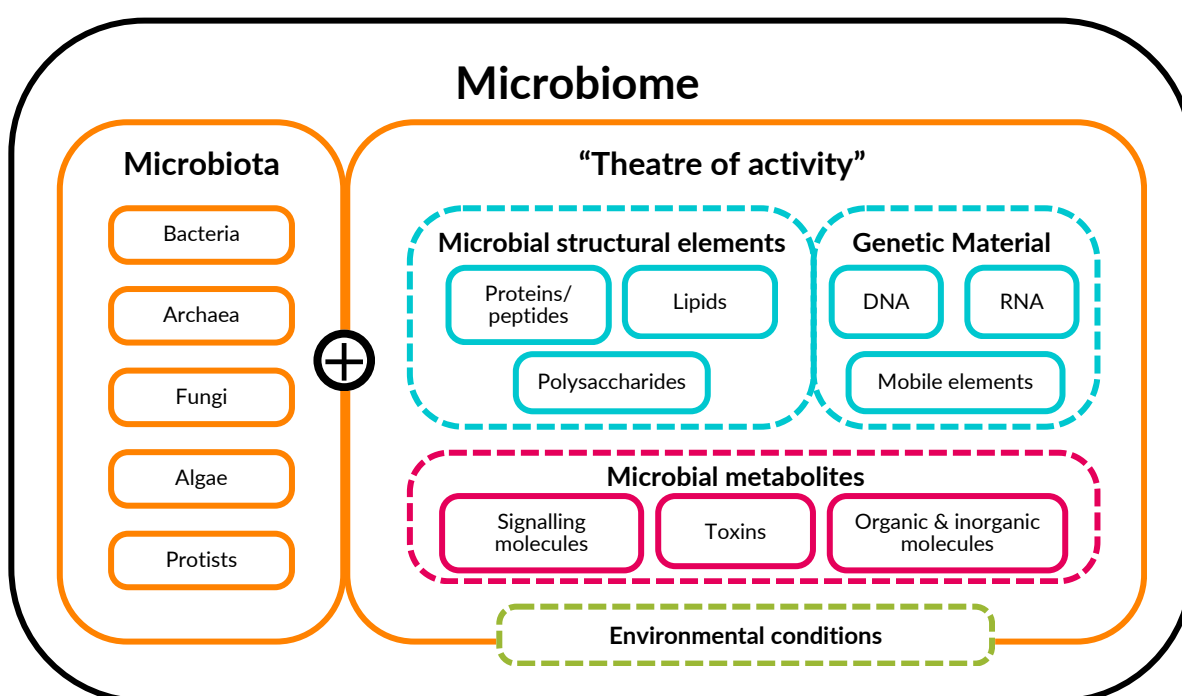


Figure 1. The composition of the microbiome containing both the microbiota and their “theatre of activity” (adapted from [3]).

and oral microbiomes [5]. The microbiome is often called a “supporting organ” due to its key role in the human body, including influencing health and the development of diseases, for example, different cancers [5,6].

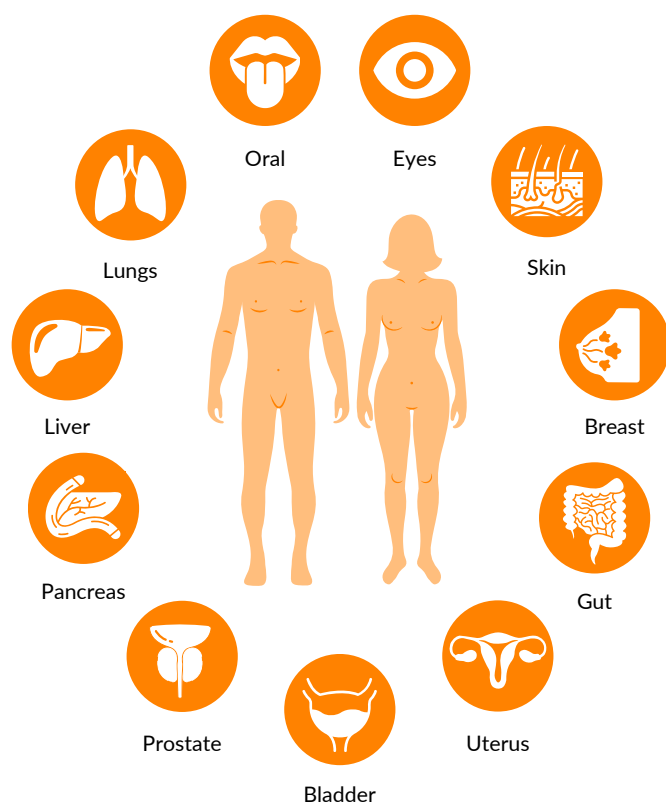


Figure 2: Examples of different microbial niches (adapted from [6]).

4. The gut microbiome

The human gastrointestinal tract is a habitat for the largest and most diverse collection of microorganisms in the human body. There are up to 38 trillion bacterial cells [7] weighing up to two kilograms [8], and approximately 3.3 million microbial genes encoded in the entire genetic repertoire of the gut microbiota [9].

Generally, the gut microbiota is composed of 6 phyla (a taxonomic category), including Firmicutes,

Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia, of which Firmicutes and Bacteroidetes are the principal types [10].

4.1 Role of the gut microbiome

The microorganisms residing in the intestine have a symbiotic relationship (a mutually beneficial relationship between two different organisms) with the human host, which is critical to maintaining balance (homeostasis) in the gut. The gut microbiota performs several essential functions, and in return, the host provides a nutrient-rich environment [11].

The gut microbiota can greatly impact health and physiological processes by interacting with one another and the body. For example, they help develop, stimulate and strengthen the immune system and the intestinal barrier to protect against invading pathogens and regulate energy metabolism and digestion, including the fermentation and absorption of undigested carbohydrates to produce metabolites such as short-chain fatty acids (SCFAs) [7,11–13]. Furthermore, they are also involved in forming essential vitamins, antigens, hormones (including oestrogen) and chemical messengers [7,10–13].

Beyond its role in nutrition and immunity, the gut microbiome can also influence the physiological functions of other organs or tissues, including the breast [14].

4.2 Factors that influence the gut microbiome

Several factors can influence the composition of gut microbiota. These include non-modifiable factors such as age, ethnicity, genetics, hormonal levels and mode of birth. They also involve environmental factors such as diet, prebiotics (fibres that feed the microbiota), probiotics (foods that naturally contain microbiota, or supplement pills that contain live active bacteria), stress, hygiene, alcohol, smoking, antibiotic use, chemotherapy, and radiation (see Figure 3) [15,16]. The most explored factors are diet, antibiotics, prebiotics, and probiotics [16].

4.3 The gut microbiome and health

The balance of the gut microbiota is closely linked to health and several diseases. A healthy gut microbiota is

characterised by a diverse community of microorganisms and a stable core microbiota, with the specific distribution of microorganisms being unique to each individual and varying [10].

Alterations to the composition and function of the gut microbiota, called dysbiosis - brought on by infectious illnesses, specific diets, or the prolonged use of antibiotics or other bacteria-destroying medications - have been associated with different diseases, and the presence or absence of specific microbes is directly linked to certain diseases. These range from gastrointestinal inflammation (e.g. inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS)) and metabolic conditions (e.g. obesity and type 2 diabetes) to neurological (e.g. depression), cardiovascular, and respiratory illnesses (e.g. asthma), and certain cancers (e.g. colorectal, stomach, pancreatic, prostate, and breast cancer) [9,10,15,17].

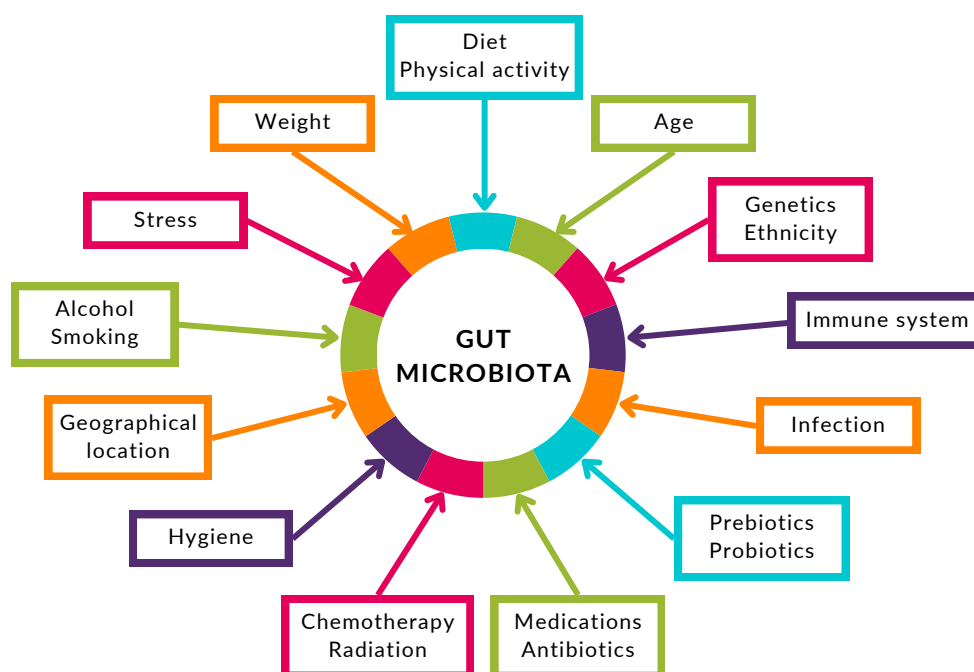


Figure 3: Factors influencing gut microbiota composition causing dysbiosis (adapted from [16]).

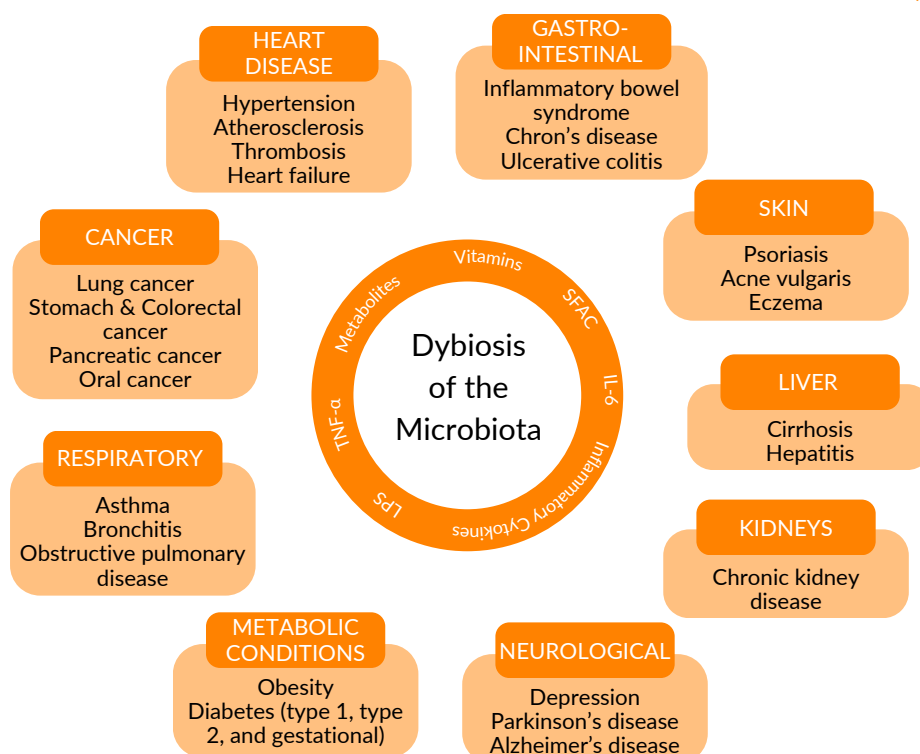


Figure 4: Microbiota dysbiosis contributes to different diseases (adapted from [10] and [17]).

4.4 The gut microbiome and breast cancer

Most microbiomes are proposed to increase cancer risk through three main mechanisms: altering the balance between cell proliferation and death, controlling the immune system, and controlling the host's metabolism [18].

The gut microbiome is an important factor in maintaining breast health, and dysbiosis of the gut microbiota has been linked to a higher risk of breast cancer [14]. This may be due to certain gut bacteria disrupting oestrogenic metabolism in the gut and/or altering the production of beneficial anticancer metabolites [16].

4.4.1 Oestrogen production

Oestrogen is a hormone that plays a crucial role in the development of many breast cancers, with higher levels of

circulating oestrogen over time increasing the risk of breast cancer, particularly in post-menopausal women [14,19]. Part of the gut microbiome, the oestrobolome, can metabolise and regulate oestrogen, altering its bioavailability and affecting oestrogen levels in the body [14,19].

Oestrogen metabolism occurs primarily in the liver, where it can be conjugated (attached) to glucuronic acid, marking it for excretion via the gastrointestinal tract. In the gastrointestinal tract, some gut bacteria produce an enzyme called β -glucuronidase (or GUS enzymes), which deconjugates (detaches) the oestrogen from the glucuronic acid, resulting in a wide array of oestrogen metabolites (free oestrogens) [20]. These oestrogen metabolites are no longer packaged in a manner compatible with excretion and are more likely to be reabsorbed into the bloodstream, potentially leading to elevated

oestrogen levels in the blood [21] and circulating to different tissues, such as the breast [16,22].

Gut dysbiosis (disturbances in the microbiota and oestrobolome) can lead to excess β -glucuronidase activity. This enzyme affects circulating oestrogen levels by catalysing deconjugation and reabsorption, thereby increasing the risk of oestrogen-responsive breast cancers [16,19]. Many microbes related to breast cancer share the β -glucuronidase enzymatic activity [23].

Interestingly, β -glucuronidase activity is modulated by diet. Diets rich in fat or protein have been associated with higher β -glucuronidase activity. In contrast, dietary fibre consumption decreases its activity, thus resulting in a decreased deconjugation and reabsorption of oestrogens and reducing circulating levels of oestrogen [16,19,21,23]. Similarly, antibiotics (e.g. ampicillin and oxytetracycline) affect the composition of the gut microbiota and have been shown to decrease the excretion of oestrogen, suggesting long-term antibiotic use may be linked to breast cancer risk [19].

Additionally, β -Glucuronidase could increase the time some endocrine-disrupting chemicals (EDCs), such as bisphenol-A (BPA), remain in the body by playing a role in their deconjugation. Some EDCs can cause changes in the gut microbiota and the metabolites they produce and may be associated with increased inflammation [22,23].

4.4.2 Microbial metabolites

The digestion and microbial products

from the gut microbiota play a significant role in breast disease development [14]. The gut microbiota secretes bioactive bacterial metabolites, including small chain fatty acids (SCFAs), secondary bile acids (SBAs), or amino acid metabolites [24]. These bacterial metabolites tend to play a cancer-protective role [16].

The production of SCFAs (mainly butyrate, propionate, and acetate), involved with fibre metabolism, has been shown to have a protective effect against the development of breast tumours [21,25,26], with low levels of SCFAs being linked to enhanced rates of breast cancers [25]. SCFAs can influence certain cancer characteristics, such as cell proliferation (increase in the number of cells), apoptosis (programmed cell death), cell invasion, gene expression, and metabolism in breast cancer, to reduce risk [16,27].

SBA metabolites are generally considered tumour inducers or promoters; however, in breast cancers, they may act as tumour suppressors [28]. SBAs, such as lithocholic acid (LCA), found in breast tissue, are initially produced by intestinal bacteria [16]. SBAs can exert anti-tumour effects, reducing breast cancer cell proliferation and aggressiveness, as well as the metastatic potential of primary tumours. Studies in mice show that this anti-tumour effect could be due to the inhibition of the epithelial-to-mesenchymal cell transition (a biological process which causes epithelial cells to undergo multiple biochemical changes which can transform into a cancer cell), or the increase of p53 expression (a

protein that acts as a tumour suppressor) [16,27,29].

Dietary amino acid metabolism produces biogenic amines with various functions. For example, cadaverine, synthesised from the essential amino acid lysine, inhibited breast cancer cell growth by inhibiting cellular proliferation, migration, invasion, and metastasis and suppressing epithelial to mesenchymal transition [16,29].

4.4.3 DNA damage

Certain intestinal microbes can disrupt genomic stability, which may trigger malignant transformation by causing cell death resistance and altering cell proliferation [16]. The gut microbiota can also cause damage to DNA by causing carcinogenic mutations, releasing toxins into host cells, or producing reactive oxygen species [16].

Another possible pathway by which several gut bacteria (e.g. *Escherichia coli*, *Staphylococcus epidermidis* and *Enterococcus faecalis*) may contribute to breast carcinogenesis is through the production of the genotoxin, such as colibactin [22,23,27]. The microbiota developed the production of genotoxins as a survival mechanism to kill hostile bacteria in its environment [18], which can also cause interstrand DNA cross-links, leading to double-strand breaks in the DNA [30]. Although DNA damage alone is not sufficient to promote breast cancer development, double-strand breaks are often considered the most serious type of DNA damage [22,23] and can lead to carcinogenesis if the DNA damage response and repair mechanism is dysregulated [18,27].

4.4.4 Immunity, inflammation and gut barrier function

The gut microbiome plays a crucial role in shaping and training the immune system [10]. A healthy gut microbiome can help enhance immune surveillance against cancer cells and reduce inflammation throughout the body, potentially reducing the risk of breast cancer [31].

Several microbes regulate specific immune processes related to cancer development. For example, *Lactococcus* spp. can maintain the cytotoxic activity of resident Natural Killer (NK) cells to modulate cellular immunity, and *Lactococcus lactis* can activate vital cells related to tumour growth (murine splenic NK cells), which enhances cellular immunity [23].

Chronic, persistent, and dysregulated inflammation has been associated with an increased risk of developing breast cancer [23]. The microbiota can stimulate and control the immune system (innate and adaptive) and mediate inflammation [18], potentially influencing breast cancer risk. Some gut microbes can help maintain healthy breast tissue by stimulating inflammatory responses; for example, the bacteria *Sphingomonas yanoikuyae* in tumorous breast tissue is reduced, leading to decreased bacterial-dependent immune cell stimulation, resulting in a permissive environment for breast tumorigenesis [23]. Dysbiosis and certain bacteria can promote chronic inflammation by producing inflammatory mediators, altering the balance of host cell proliferation and

death, and triggering uncontrolled innate and adaptive immune responses associated with cancer progression [16,23,32].

The gut barrier acts as a protective layer, with the gut microbiota reinforcing the intestinal barrier to prevent harmful substances from entering the bloodstream. The gut microbiota does this by stimulating mucus production by intestinal epithelial cells and strengthening the junctions between them, competing with pathogenic microbes for binding to the intestinal mucosa and stimulating the secretion of the antibody immunoglobulin A (IgA) by immune cells present in the intestine [16,22,23]. Dysbiosis can reduce the bacterial diversity that maintains the mucus lining, which can increase gut barrier permeability, allowing toxins and other harmful compounds to enter circulation, inciting both local and systemic inflammatory responses and potentially impacting breast cancer risk [33]. In addition, IgA recognises and regulates the composition of the gut microbial community, limiting the invasiveness of potentially dangerous bacterial species [23]. Dysbiosis of the gut microbiota can alter IgA secretion and response, leading to unregulated bacterial growth, which may influence breast cancer risk [10,34].

4.4.5 Adiposity and obesity

The gut microbiota has been linked to increased adiposity and obesity, which are known breast cancer risk factors via their effect on oestrogen levels [16,23]. Postmenopausal overweight and obese women have a higher risk of breast cancer compared to women of a healthy

weight [23]. Not only is the gut microbiota less diversified in individuals who are obese [22,23], but gut microbial dysbiosis can lead to the development of adiposity and obesity [16,19,23]. Modulating the gut microbiota to ensure normobiosis could be an approach to target obesity and its associated breast cancer risk [16].

5. Other microbiomes and breast cancer

Other microbiomes, including the breast, oral, and skin microbiomes, have also been studied in relation to breast cancer risk.

5.1 The breast microbiome and breast cancer

Although it was previously thought that breast tissue was sterile, it is now known that breast tissue, which is made up of fatty tissue with an extensive vascular system and lymphatic drainage, is a favourable environment for the growth of bacteria and has a diverse and unique microbiome [14,31,35].

The main microbes found in the breast microbiota belong to 7 different phyla: Proteobacteria, Firmicutes, Actinobacteria, Bacteroidetes, Deinococcus-Thermus, Verrucomicrobia, and Fusobacteria [23], of which Proteobacteria and Firmicutes are the most abundant, which may be due to their capability to adapt to the fatty acid environment in the breast tissue [14,23,35]. The breast microbiome may originate from different routes, either by translocation from the gut via the bloodstream and/or from the skin via the nipple-areolar by nipple-

mouth contact during breastfeeding or sexual contact [23,35,36].

Comparisons of breast tissue from healthy people and breast cancer patients, as well as collections of nipple aspirate fluid (a natural secretion produced by breast epithelial cells), have shown different bacterial profiles [14,23,35,37]. Notably, in the breast tissue of breast cancer patients, there were more *Bacillus*, *Staphylococcus*, *Enterobacteriaceae*, *Comamonadaceae*, and *Bacteroidetes* [14,23,37]. These bacteria can cause DNA damage, and some species are known for their cancer-promoting properties, such as *Escherichia coli* [23,35]. Additionally, there was a decrease in some lactic acid bacteria, known for their beneficial health effects, including anti-carcinogenic properties [23]. This may indicate that dysbiosis of the breast microbial community may be associated with breast cancer [23].

Changes in the composition of the breast microbiota may modulate the risk of breast cancer development and progression; however, it is unclear if these changes are a consequence or a cause of breast carcinogenesis and whether specific microbes are responsible for breast carcinogenesis [23,27,31]. It has been proposed that the breast microbiome may help maintain healthy breast tissue by stimulating the local immune microenvironment and degrading carcinogens [23,27,31]. There is also potential that unique viral, bacterial, fungal and parasitic signatures with distinct patterns may be related to different breast cancer subtypes;

however, further investigation is needed [23,31,38].

In addition, the microbiota of the breast and breast milk can influence the development of healthy infant gut microbiota and women's health. Dysbiosis of bacteria in the mother's breast could induce mastitis. Furthermore, it may influence infant growth, metabolic development, appropriate microbial colonisation, and immune system maturation during the breastfeeding period, which, in turn, may modulate health risk later in life, including the risk of developing cancer [14,27].

5.2 The skin microbiome and breast cancer

The human skin is composed of different, unique niches of microbes. Breast skin offers a physical barrier protecting the breast tissue from environmental triggers [39]. The skin microbiota generally contains Actinobacteria, Bacteroidetes, Cyanobacteria, Firmicutes, and Proteobacteria [10].

Dysbiosis of the skin microbiota has been linked to breast skin conditions, such as psoriasis or eczema, and skin cancer, by provoking chronic inflammation [39]. While some studies have shown there is no link between skin microbiota dysbiosis and breast cancer, others have highlighted that breast skin swabs from breast cancer patients are enriched in *Staphylococcus*, which has been associated with carcinogenesis [37,39]. It is still unknown whether skin microbiota

dysbiosis affects breast tissue and breast cancer development, and more evidence is needed [39].

5.3 The oral microbiome and breast cancer

The oral microbiota, the microbial community of the mouth, can be found in multiple habitats, including the saliva, tongue, tooth surface, gums, inner lining of the cheeks (buccal mucosa), palate, and plaque [10]. Generally, the main bacteria found are from the phyla Firmicutes, Proteobacteria, Bacteroidetes, Actinobacteria, and Fusobacteria [10], with an abundance of the species *Streptococcus* in the oral cavity and *Haemophilus* in the buccal mucosa [21].

There may be a link between the oral microbiota and the risk of breast cancer, as it was found that women with periodontal disease (disease of the gum), a disease caused by specific bacteria, have a higher risk of breast cancer, particularly in post-menopausal individuals [24,31]. However, this area lacks data, and further studies are needed to investigate the connection between the oral microbiome and breast cancer [31].

10. Conclusions

The findings from this review show that the human microbiome is an essential factor in maintaining breast health and could modulate the risk of developing breast cancer. Dysbiosis of the gut microbiota has been linked to a higher risk of breast cancer, possibly due to

certain gut bacteria disrupting oestrogenic metabolism, causing DNA damage, impacting immunity and inflammation, and/or altering the production of beneficial anticancer metabolites. Other microbiomes, such as the breast, skin or oral microbiomes, may also influence breast cancer risk; however, further research is needed to establish their link to breast cancer development.

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About Breast Cancer UK

Who we are?

Breast Cancer UK aims to prevent breast cancer through scientific research, collaboration, education and policy change. We educate and raise awareness of the risk factors for breast cancer and provide practical information to help people reduce these risks. We campaign to ensure government policies support the prevention of breast cancer. And we fund scientific research that helps to better understand what risk factors contribute to breast cancer, and how to address them. For further information on breast cancer risk factors please visit our website www.breastcanceruk.org.uk

To view this information in a more accessible format or to provide feedback, please contact us.





This review is for information purposes only and does not cover all breast cancer risks. Nor does it constitute medical advice and should not be used as an alternative to professional care. If you detect a lump or have any concerns, seek advice from your GP. Breast Cancer UK has made every effort to ensure the content of this leaflet is correct at the time of publishing but no warranty is given to that effect nor any liability accepted for any loss or damage arising from its use.

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We welcome your feedback, if you have any comments or suggestions about this review please contact us at info@breastcanceruk.org.uk or on 0208 1327088.

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