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MICROBIOTA PROFILE VARIATION AND BREAST CANCER: SYSTEMATIC REVIEW

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ABSTRACT

Background: *The microbiota is known to have a metabolic role in a physiological process or a pathological process. Microbiota identification through biomolecular techniques in certain clinical situations continues to develop.The microbiota population in breast cancer tissue is thought to have a role in the tumor microenvironment supporting the ability to develop. Understanding the relationship between microbiota and breast cancer is still unclear with a heterogeneous profile. The aim of the study is to explain the major microbiota profile of breast cancer and consider possible biological connections among them.*

Objectives*: to determine differences in microbiota profiles in breast cancer patients compared with normal and to analyze the role of microbiota in the development of breast cancer.*

Method: *this literature review investigated the different composition of microbiota profile in breast cancer patients compared with normal. Following the PRISMA guideline, the study was carried out by database literature searching using the PICO method on Pubmed and Google Scholar databases. Searches are restricted to open access research articles from the last 5 years. Critical appraisals are carried out for quality assessment.*

Results: *there were 145 articles matched to the keywords, and 17 passed filtering and screening are included in the review. Some of the major microbiota found in breast cancer patients are firmicutes, proteobacteria, actinobacteria, and bacteroidetes. The microbiota profile depends on the cancer subtype, menopausal history, and tumor severity. The microbiota plays a role in the inflammatory response to its metabolite products and modulates hormonal changes that may enhance tumor survival.*

Keywords : *breast; cancer; microbiota*

RINGKASAN

Latar Belakang: *Mikrobiota diketahui memiliki peran metabolik dalam proses fisiologis maupun patologis. identifikasi mikrobiota melalui teknik biomolekuler pada keadaan klinis tertentu masih terus berkembang. Perkembangan keilmuan mengenai mikrobiota tubuh sangat berkembang seiring dengan perkembangan teknologi molekuler. Populasi mikrobiota yang juga ditemukan pada jaringan kanker payudara diduga memiliki peranan dalam mendukung lingkungan mikro tumor sehingga sel tumor memiliki kemampuan untuk berkembang. Hingga saat ini pengetahuan mengenai keterkaitan mikrobiota dan kanker payudara belum dapat dijelaskan secara pasti dengan hasil penelitian yang heterogen. Penelitian ini diharapkan dapat menjelaskan profil*

mikrobiota kanker payudara dan mempertimbangkan kemungkinan mekanisme keterkaitan biologisnya.

Tujuan Penelitian: *untuk mengetahui perbedaan profil mikrobiota pada pasien kanker payudara dibandingkan dengan payudara normal serta menganalisis peranan mikrobiota terhadap perkembangan penyakit kanker payudara.*

Metode Penelitian: *Telaah literatur ini dilakukan untuk mengetahui profil mikrobiota pada pasien kanker payudara dibandingkan dengan payudara normal. Penelitian dilakukan dengan pencarian pustaka menggunakan basis data menggunakan metode PICO pada database Pubmed dan google scholar. Pencarian dibatasi untuk artikel penelitian yang memiliki akses terbuka luaran 5 tahun terakhir. Critical appraisal dilakukan untuk penilaian kualitas studi.*
Hasil: *terdapat 145 penelitian yang sesuai dengan kata kunci pencarian, 18 artikel memenuhi kriteria penyaringan dan digunakan pada penelitian ini. Beberapa mikrobiota mayor yang ditemukan pada pasien kanker payudara adalah firmicutes, proteobacteria, actinobacteria, firmicutes dan bacteroidetes. Profil mikrobiota tersebut bergantung pada subtipe kanker, riwayat menopause, tingkat keparahan tumor. Microbiota tersebut berperan dalam respons peradangan terhadap produk metabolitnya dan memodulasi perubahan hormonal yang dapat meningkatkan kelangsungan hidup tumor.*

Kata kunci*: mikrobiota; kanker; payudara*

Introduction

The human body contains at least 100 trillion microbes which are the body's microbiota and begin to develop from birth. The microbiota colonizes the mucous lining of several organs, especially in the digestive system (70%). Microbiota has a role in macronutrient metabolism, plays a role in energy retrieval and storage, and interacts with the immune system to form immunity.it is known that microbiota have been associated with overall health condition nor pathological. Dependence on the composition of the gut microbiota (dysbiosis) can affect the local organs as well as affect systemic functions. Microbiota dysbiosis is known to be a risk factor for several diseases, including cancer.[1]

Some bacterial colonization known to play a role in several cancers, including *Helicobacter pylori* colonization in gastric cancer, increased populations of *Bacteroides fragilis, Fusobacterium nucleatum, P.anaerobius* are known to play a role in colorectal cancer, while the microbiota that play a role in breast cancer is still heterogeneous. Since the discovery of the microbiota population in the breast, it is known that there is an interaction between the gut microbiota and the breast microbiota that triggers the development of breast cancer. The microbiota can originate from the spread through the lymphatic vessels, and from the nipples during lactation. The main phylum found in normal breast tissue of women with a history of breastfeeding is the Proteobacteria phylum.[2,3,4]

In recent times, scientists have studied the relationship between human microbiome signatures and carcinogenesis, which is called the oncobiome. It has been known that the microbiota in the tumor microenvironment has a role in carcinogenesis, cancer development and influences response to anti-cancer treatment. Some microbiota are known to increase the synthesis and metabolism of the estrogen hormone which can increase the development of breast cancer. [5,6]

METHOD

Study Design

This research was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The research question, inclusion and exclusion criteria were determined using PICO structure (Patient, Intervention/exposure, comparison, outcome and Study Design). A systematic review was conducted on the PUBMED and Google Scholar database in the year 2017 to 2022 to identify research that is relevant to the questions according to PICO. The search syntax used in this study uses keywords 'microbiota' OR 'microbiome' AND 'breast cancer' (table 1).

Table 1. Keywords for literature search

Database	Keywords	Limitation
PUBMED	((microbiota)OR (microbiome)) AND (breast cancer)	Clinical trial, RCT, human
Google Scholar	Microbiota OR microbiome breast AND cancer	All in title

Study Selection and data extraction

Primary screening was conducted independently by two reviewers (AN, RG) using the web application Rayyan. Screenings are performed to exclude the duplicate, and to access the eligibility of the articles. Two reviewers independently extracted the data from eligible studies (AN, RG). Where there were conflicts, consensus was achieved through discussion.

Quality assessment

Journal analysis of this systematic review uses the critical appraisal method. To avoid bias and subjective understanding, the literature obtained will be analyzed using a study quality assessment based on JBI (accessed via https://jbi.global/critical-appraisal-tools). The literature included in the research must at least meet a score of 50% of the checklist questions. Comprehensive analysis is carried out by assessing the title, abstract and full manuscript content of the article. Data synthesis was then carried out descriptively.

Results

There were a total of 145 literature that matched the keywords in the 2 databases used in the literature search (table 1). Literature that has been obtained from search engines (databases) is then filtered for duplication of literature using the Rayyan intelligence device. Seven duplicates were found and excluded. A total of 138 literature was then filtered according to the research objectives based on title and abstract. A total of 90 research articles corresponding to the studies were then assessed for eligibility. A total of 17 studies included in this systematic review (figure 2).

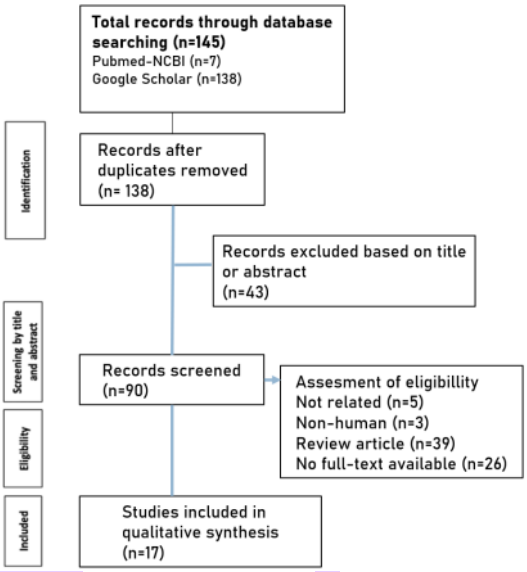

Figure 2. PRISMA diagrams of literature review

Discussion

Microbiota in breast cancer patient

Breast cancer is categorized into several subtypes based on molecular characteristics, namely luminal A, luminal B, HER2 positive, and triple negative. Breast cancer microbiota population has heterogeneity based on variations in histological appearance, tumor grade, lymph node status, and the presence of predictive markers such as estrogen receptors and human epidermal growth factor receptor 2 (HER2). The microbial population can be influenced by various factors, including hormonal status, age at menarche, breast cancer subtype, and age. Major microbiota found in this study are represented in table 2.

Table 2. The major microbiota profile studies in breast cancer patients

Authors	Methodology	Population	Microbiota profiles
Thompson, et.al (2017)[7]	16S rRNA sequencing	Non cancerous tissue, HER2+, ER+, and triple negative breast cancer	Proteobacteria (48%), Actinobacteria (26.3%), Firmicutes (16.2%)
Alice, et.al (2021)[9]	16S rRNA sequencing	Fresh-frozen breast cancer tumor; HER2+, ER+	Proteobacteria, with either Firmicutes or Actinobacteria
Shi, et.al (2019)[15]	16S rRNA sequencing	Frozen fecal sample of breast cancer patient : HER2+, ER+, HER2-, ER-	Actinobacteria bacteroidetes, firmicutes, fusobacteria, proteobacteria
Hieken, et.al (2022)[16]	16S rRNA sequencing	Benign and malignant breast tissue	Firmicutes, staphylococcus
Dubigeon, et. al (2021)[17]	16S rRNA sequencing	Fecal microbiota composition patients	Firmicutes, Clostridium Blautia

		with breast cancer and healthy women	
Kim, et.al (2021)[20]	16S rRNA sequencing	Breast cancer tissue and normal tissue	Proteobacteria and Firmicutes, Actinobacteria
Zhijun, et.al (2022)[21]	16S rRNA sequencing	Stool specimen of non-malignant and malignant breast cancer patient, and healthy patient	Escherichia, Peptoniphilus, Bilophila, Lactobacillus, and Porphyromonas
Lasagna, et.al (2022)[22]	16S rRNA sequencing	Stool specimen from breast cancer patient ER/PgR-positive and HER2-negative	Firmicutes and Bacteroidetes
Wenhui, et.al (2022)[23]	16S rRNA sequencing	fecal samples from normal controls, breast cancer patients	Bacteroidetes, firmicutes and proteobacteria, fusobacteria, actinobacteria
Maryann, et.al (2022)[24]	16S rRNA sequencing	fecal samples from normal controls, breast cancer patients	Blautia and ruminococcaceae, Bifidobacterium animalis

Crosstalk of microbiota and breast cancer

The understanding of the human microbiome is known to have effects involving hormonal changes, metabolites, and immunologic pathways which are influences in carcinogenesis. They might contribute to evading cell death, influences in lipid metabolism, regulate and produce hormonal products, sustaining the cancer cell to grow, leading to cancer progression.[9] Several studies have shown that differences in age, BMI, cancer subtype, and menopausal status can affect the microbiota profile of breast cancer patients.[9,10] Since the population of breast microbiota in lactating women is known, various researchers have paid attention to how its profile and how the dysbiosis of microbiota could affect breast cancer. This diversity of microbiota study showed that interconnection between the microbiota and breast cancer is a complex process and multifactorial.

In this study, it was found that *firmicutes, proteobacteria, actinobacteria, bacteroidetes and blautia* are the major microbiota found in patients with breast cancer with various potencies. Increased Firmicutes and bacteroidetes are known to increase the occurrence of fibrosis in breast cancer. Firmicutes and Bacteroidetes are known to be a bacterium that has a relationship with fat (adipocytes derived bacteria).[11,12,13,16,17] They are known to modulate releases of serine palmitoyl transferase enzymes in the formation of sphingolipids from ceramide sphingolipids. Upregulation of fat is known to be a source of energy for tumor growth in the process of carcinogenesis.in addition, Firmicutes and Bacteroidetes are involved in the colonic metabolism of indigestible nutrient dietary fibers and polyphenols. [11,12,14,16,17]

Gut Microbiota can play a role in the regulation of the estrogen hormone, especially in menopausal patients. The microbes can be estrobolome which can activate enzymes that are capable in conjugating estrogen metabolites for excretion and circulation in active form. Some microbiota such as firmicutes, proteobacteria, Clostridium and Blautia sp are known to have capacity in catalyze the hydrolysis of inactive glucuronidated estrogens through the β-glucuronidases and β-glucosidases enzymes. [12,13,20] This can increase the reabsorption of the active

form of estrogen through enterohepatic circulation which can cause carcinogenesis of breast cancer. Increases in systemic estrogen levels contribute to increased breast cancer risk and its severity. The gut microbes can also synthesize estrogen-like compounds or estrogen mimics break down by the various potencies. [12,13,20,23,24]

In conclusion, the expression of microbiota profile both in gut or its tissue might not be generalized because it is multifactorial based on patient characteristics; age, menopausal states, BMI, tumor grade and subtype. The study suggests that the major microbiota that show increases in breast cancer are *firmicutes*, *proteobacteria, actinobacteria, bacteroidetes and blautia* and play a role in breast cancer development in a different manner.

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Conflict of interests
The authors have no conflict of interest

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