rom_Faecal_Specimen_and_Cancerous_Breast_Tissue_A_Comprehens.pdf

by Universitas Ahmad Dahlan Yogyakarta 23

Submission date: 22-Jan-2024 10:53AM (UTC+0700)
Submission ID: 2275530281
File name: rom_Faecal_Specimen_and_Cancerous_Breast_Tissue_A_Comprehens.pdf (251.38K)
Word count: 2898
Character count: 17200

REVIEW ARTICLE

INDONESIAN JOURNAL OF CANCER

Major Microbiota Profile of Breast Cancer From Faecal Specimen and Cancerous Breast Tissue: A Comprehensive Systematic Review

Annisa Annisa [1*], Rachma Greta [1], Solikhah Solikhah [2]

[1] Department of Histology, Faculty of Medicine, Universitas Ahmad Dahlan, Yogyakarta, Indonesia

[2] Public Health Science Faculty, Universitas Ahmad Dahlan, Yogyakarta, Indonesia

ARTICLE INFO

Received : 20 February 2023
Reviewed : 13 March 2023
Accepted : 24 May 2023

Keywords:
breast cancer, microbiota

Corresponding author:
Annisa Annisa
Department of Histology,
Faculty of Medicine, Universitas
Ahmad Dahlan, Yogyakarta, Indonesia
annisa@med.uad.ac.id

ABSTRACT

Background: The microbiota population in breast cancer tissue is known to have a crucial role in the tumor microenvironment supporting developmental ability. Despite a heterogeneous profile, the relationship between microbiota and breast cancer is still not fully understood. Therefore, this study aimed to explain the major microbiota profile associated with breast cancer and explore potential biological connections.

Methods: Following the PRISMA guidelines, the literature review investigated the diverse composition of microbiota profiles in breast cancer patients compared to those in normal conditions. Utilizing the PICO framework, a comprehensive search was conducted on the Pubmed and Google Scholar databases. The searches were restricted to open-access articles from the last 5 years. Additionally, critical appraisals are conducted for quality assessment.

Results: A total of 145 articles were identified using the relevant keywords, out of which 17 successfully passed filtering and screening for inclusion in the review. Major microbiota observed in breast cancer patients included *firmicutes, proteobacteria, actinobacteria, and bacteroidetes*. The microbiota profile was influenced by factors such as cancer subtype, menopausal history, and tumor severity. These microorganisms play a role in the inflammatory response to their metabolite products and modulate hormonal changes, potentially enhancing tumor survival.

Conclusions: Generalizing the expression of microbiota profile both in the gut or its tissue might be challenging due to its multifactorial nature, dependent on patient characteristics such as age, menopausal status, BMI, tumor grade, and subtype. The study suggests that the major microbiota that shows increased prevalence in breast cancer include *firmicutes, proteobacteria, actinobacteria, bacteroidetes, and blautia,* each playing a distinct role in the developmental process.

INTRODUCTION

The human body contains at least 100 trillion microbes, collectively known as microbiota, which begins its development from birth. These microbes colonize the mucous lining of several organs, especially in the digestive system (70%). The microbiota plays a crucial role in macronutrient metabolism, energy retrieval, and storage, as well as actively interacting with the immune system to form immunity. It is recognized that the composition of the gut microbiota, termed dysbiosis, can impact local organs and systemic functions, thereby influencing overall health conditions, both normal and pathological. Dysbiosis is identified as a risk factor for several diseases, including cancer [1].

Some bacterial colonizations are implicated in several cancers. For instance, *Helicobacter pylori* colonization is associated with gastric cancer, and increased populations of *Bacteroides fragilis, Fusobacterium nucleatum, and Peptostreptococcus anaerobius* play a role in colorectal cancer. In contrast, the microbiota linked with breast cancer remains heterogeneous [2,3]. Since the discovery of the microbiota population in the breast, it has been recognized that interaction between the gut and the breast microbiota contributes to the development of breast cancer. These microorganisms may originate from the spread through the lymphatic vessels or the nipples

during lactation. The main phylum discovered in normal breast tissue of women with a history of breastfeeding is the Proteobacteria phylum [4–6].

In recent times, scientists have studied the relationship between human microbiome signatures and carcinogenesis, which is called the microbiome. It has been discovered that the microbiota in the tumor microenvironment plays a role in carcinogenesis, and cancer development, influencing response to anti-cancer treatment. Some microbiota are known to increase the synthesis and metabolism of the estrogen hormone, thereby enhancing the development of breast cancer [7,8].

Several published systematic reviews focused on the significance of the microbiome in the development and control of breast cancer cells. However, there are discrepancies and no conclusive results to explain the direct connectivity of breast cancer to specific microbiota [9]. This may be attributed to the study bias regarding the challenges in establishing stronger interconnectivity between these microorganisms and the host due to the heterogeneous patient characteristics [10]. The study aimed to elucidate the major microbiota profile of breast cancer and explore potential biological connections.

METHODS

Study design

This study was conducted according to the PRISMA guidelines. The study question, as well as inclusion and exclusion criteria, were determined using PICO structure (Patient; Breast cancer, Intervention/exposure; microbiota, comparison; healthy woman/non-cancerous breast, outcome; cancer development). A systematic review was conducted on the PUBMED and Google Scholar databases ranging from 2017 to 2022 to identify relevant articles. The keywords used in the search process were '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. This aimed to exclude the duplicates and to assess the eligibility of the articles. Data extraction from eligible studies was performed by 2 reviewers (AN, RG), and any conflicts were resolved by consensus achieved through discussion.

Quality assessment

This systematic review adopted the critical appraisal method for journal analysis. To avoid bias and subjective understanding, the literature obtained was analyzed using a study quality assessment based on JBI, accessed via https://jbi.global/critical-appraisal-tools. The articles included were required to meet at least a score of 50% on the checklist questions. A comprehensive analysis was conducted by assessing the title, abstract, and full content of the manuscript. Data synthesis was then performed descriptively.

RESULTS

A total of 145 literature matching the designated keywords were identified in the 2 databases used for the search, as presented in **Table 1.** Following the utilization of the Rayyan intelligence device, 7 duplicates were identified and subsequently excluded. The remaining 138 pieces of literature were filtered according to the study objectives, using title and abstract as criteria. Subsequently, a total of 90 articles corresponding to the scope were subjected to further eligibility assessment. Finally, 17 studies were included in this systematic review **(Figure 1).**

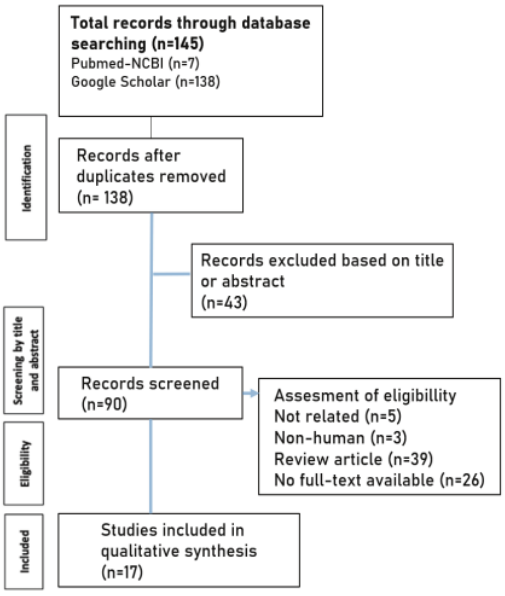

Figure 1. PRISMA diagrams of literature review

Microbiota in breast cancer patient

Breast cancer is categorized into several subtypes based on molecular characteristics, namely luminal A, luminal B, human epidermal growth factor receptor 2 (HER2) positive, and triple negative. The microbiota

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

Authors	Methodology	Hormonal Status	Age (mean)	Population	Microbiota profiles
Thompson, et.al (2017)[11]	16S rRNA sequencing	HER2+, ER+, triple negative	-	Cancerous breast tissue	Proteobacteria (48%), Actinobacteria (26.3%), Firmicutes (16.2%)
Tzeng, et.al (2021)[12]	16S rRNA sequencing	HER2+, ER+	57	Fresh-frozen breast cancer tumor	Proteobacteria, with either Firmicutes or Actinobacteria
Shi, et.al (2019)[13]	16S rRNA sequencing	HER2+, ER+,	-	Frozen fecal sample of breast cancer patient	Actinobacteria Bacteroidetes, firmicutes, Fusobacteria, Proteobacteria
Hieken, et.al (2022)[14]	16S rRNA sequencing	ER+	60	Benign and malignant breast tissue	Firmicutes, staphylococcus
Dubigeon, et. al (2021)[15]	16S rRNA sequencing	HER2-, ER+	63	Fecal microbiota breast cancer patient	Firmicutes, Clostridium Blautia
Kim, et.al (2021)[16]	16S rRNA sequencing	ER+ (59,6%), ER-(40,4%), HER2- (70,2%), HER2+(29,8), PR+(53,2%), PR- (46,8%)	54	Breast cancer tissue	Proteobacteria and Firmicutes, Actinobacteria
Ma Zhijun, et.al (2022)[17]	16S rRNA sequencing	-	-	Stool specimen of malignant breast	Escherichia, Peptoniphilus, Bilophila, Lactobacillus, and Porphyromonas
Lasagna, et.al (2022)[18]	16S rRNA sequencing	ER/PR+ and HER2-		Stool specimen from breast cancer patient	Firmicutes and Bacteroidetes
Wenhui, et.al (2022)[19]	16S rRNA sequencing	ER+ (71,9%), ER-(28,1%), HER2- (28,1%), HER2+(71,9%), PR+(31,2%), PR- (68,8%)	53	fecal samples from normal controls, breast cancer patients	Bacteroidetes, firmicutes and proteobacteria, fusobacteria, actinobacteria
Maryann, et.al (2022)[20]	16S rRNA sequencing	ER/PR+	64	fecal samples from normal controls, breast cancer patients	Blautia and ruminococcaceae, Bifidobacterium animalis

rRNA: ribosomal RNA; ER: Estrogen Receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor-2

population in breast cancer had heterogeneity, influenced by variations in histological appearance, tumor grade, lymph node status, and the presence of predictive markers such as estrogen receptors and HER2. Several factors, including hormonal status and breast cancer subtype, can influence the dynamics of the microbiota population. Microorganisms play essential roles in disease, impacting both the intestine and extra-intestine in different ways. Several references state that the microbiota of the breast in the mammary duct was obtained through the lactation process. Activation of immune cells has the potential to transfer microbiota from breast tissue to the intestine or vice versa through the enteromary route. Through metabolic regulation, immune cell response, and inflammatory processes, the microorganisms are known to have local and systemic impacts on the process of carcinogenesis. Therefore, the most frequently used method for examining microbiota in breast cancer includes analyzing both breast tissue and stool specimens. The major microbiota found in this study are represented in **Table 2.**

DISCUSSION

The effect of the human microbiome on hormonal changes, metabolites, and immunologic pathways, crucial in carcinogenesis is well-documented. These factors may contribute to cell death evasion, lipid metabolism alteration, and regulation of hormonal products, sustaining cancer cell growth and progression [9]. Several studies have shown that age differences, Body Mass Index (BMI), cancer subtype, and menopausal status significantly affect the microbiota profile of breast cancer patients [9,10]. The well-documented breast microbiota in lactating women has prompted a study into its potential impact on breast cancer, showing a complex and multifactorial interconnection between microbiota and the disease.

The identified microbiota in breast cancer patients include *Firmicutes, Proteobacteria, Actinobacteria, Bacteroidetes, and Blautia*, each with varying degrees of influence. Elevated level of *Firmicutes* and *Bacteroidetes* correlates with increased fibrosis, given

their connection to adipocytes and fat metabolism [11,12,21,13,24,25]. These bacteria modulate releases of serine palmitoyl transferase enzymes in the formation of sphingolipids from ceramide sphingolipids. The upregulation of fat is known to be a source of energy for tumor growth in the process of carcinogenesis. Furthermore, *Firmicutes and Bacteroidetes* play a role in the colonic metabolism of indigestible nutrients, dietary fibers, and polyphenols [11,21,22,24,25].

The impact of Gut Microbiota extends to the regulation of the estrogen hormone, especially in menopausal patients. Microbes, including estrobolome, activate enzymes conjugating estrogen metabolites for excretion and circulation in active form. Specific microbiota such as *Firmicutes, Proteobacteria, Clostridium, and Blautia*, can catalyze the hydrolysis of inactive glucuronidated estrogens through β-glucuronidases and β-glucosidases enzymes [11,12,21]. This process increases the reabsorption of the active form of estrogen through enterohepatic circulation, potentially contributing to the carcinogenesis of breast cancer. Elevated systemic estrogen levels contribute to increased risk and severity of the disease. The gut microbes can also synthesize estrogen-like compounds or break down estrogen mimics by the various potencies [11,12,15,21,28].

This study provided information to explain the connection of microbiota to breast cancer based on current investigation through heterogeneous data. The complex relationship between microbiota and the disease comprises roles in metabolite processes, hormonal regulation, and immune pathways. To confirm the molecular pathways, further investigation through large-scale, specific randomized controlled trials engaging breast cancer patients is essential.

CONCLUSIONS

The expression of microbiota profile either in gut or tissue was not generalized due to its multifactorial nature, influenced by various patient characteristics such as age, menopausal status, BMI, tumor grade, and subtype. The study suggested that the major microbiota associated with increased instances of breast cancer were *Firmicutes, Proteobacteria, Actinobacteria, Bacteroidetes, and Blautia*. These microbial components play distinct roles in the development of the disease.

DECLARATIONS

Competing of interests

The authors have no conflict of interest.

Acknowledgments

Not applicable

Funding

This study was supported by Lembaga Penelitian dan Pengabdian Kepada Masyarakat (LPPM) Universitas Ahmad Dahlan Yogyakarta.

REFERENCES

1. Zhang J, Xia Y, Sun J. Breast and gut microbiome in health and cancer. Genes Dis. 2020;8(5):581–589.
2. Pandey H, Tang DWT, Wong SH, Lal D. Gut Microbiota in Colorectal Cancer: Biological Role and Therapeutic Opportunities. Cancers (Basel). 2023;15(3):866.
3. Wong, S.H. Targeting Gut Microbiota in Colorectal Cancer. In: Yu, J. (eds) Microbiome in Gastrointestinal Cancer. Springer, Singapore; 2023. Available from: https://doi.org/10.1007/978-981-19-4492-5_16
4. Khan AA, Sirsat AT, Singh H, Cash P. Microbiota and cancer: current understanding and mechanistic implications. Clin Transl Oncol. 2022;24(2):193–202. d
5. Urbaniak C, Cummins J, Brackstone M, et al. Microbiota of human breast tissue. Appl Environ Microbiol. 2014;80(10):3007–3014.
6. Cheng WY, Wu C, Yu J. The role of gut microbiota in cancer treatment: friend or foe?. Gut. 2020;69:1867–1876.
7. Khan AA, Sirsat AT, Singh H, Cash P. Microbiota and cancer: current understanding and mechanistic implications. Clin Transl Oncol. 2022 Feb;24(2):193–202.
8. Wang N, Sun T, Xu J. Tumor-related Microbiome in the Breast Microenvironment and Breast Cancer. J Cancer. 2021;12(16):4841–4848.
9. Toumazi D, El Daccache S, Constantinou C. An unexpected link: The role of mammary and gut microbiota on breast cancer development and management (Review). Oncol Rep. 2021 May;45(5):80.
10. Alpuim CD, Nobre JG, Batista MV, et al. Human Microbiota and Breast Cancer-Is There Any Relevant Link?-A Literature Review and New Horizons Toward Personalised Medicine. Front Microbiol. 2021;12:584332.
11. Thompson KJ, Ingle JN, Tang X, et al. A comprehensive analysis of breast cancer microbiota and host gene expression. PLoS One. 2017 Nov 30;12(11):e0188873.
12. Tzeng A, Sangwan N, Jia M, et al. Human breast microbiome correlates with prognostic features and immunological signatures in breast cancer. Genome Med. 2021 Apr 16;13(1):60.
13. Shi J, Geng C, Sang M, et al. Effect of gastrointestinal microbiome and its diversity on the expression of tumor-infiltrating lymphocytes in breast cancer. Oncol Lett. 2019 Jun;17(6):5050–5056.

14. Hieken TJ, Chen J, Chen B, et al. The breast tissue microbiome, stroma, immune cells and breast cancer. Neoplasia. 2022;27:100786.
15. Bobin-Dubigeon C, Luu HT, Leuillet S, et al. Faecal Microbiota Composition Varies between Patients with Breast Cancer and Healthy Women: A Comparative Case-Control Study. Nutrients. 2021;13(8):2705.
16. Kim HE, Kim J, Maeng S, et al. Microbiota of Breast Tissue and Its Potential Association with Regional Recurrence of Breast Cancer in Korean Women. J Microbiol Biotechnol. 2021;31(12):1643–1655.
17. Ma Z, Qu M, Wang X. Analysis of Gut Microbiota in Patients with Breast Cancer and Benign Breast Lesions. Pol J Microbiol. 2022;71(2):217–226.
18. Lasagna A, De Amici M, Rossi C, et al. The Bio-Diversity and the Role of Gut Microbiota in Postmenopausal Women with Luminal Breast Cancer Treated with Aromatase Inhibitors: An Observational Cohort Study. Pathogens. 2022;11(12):1421.
19. Wenhui Y, Zhongyu X, Kai C, et al. Variations in the Gut Microbiota in Breast Cancer Occurrence and Bone Metastasis. Front Microbiol. 2022;13:894283.
20. Kwa M, Ruggles KV, Novik Y, et al. Evaluation of the Gut Microbiome and Sex Hormones in Postmenopausal Women with Newly Diagnosed Hormone Receptor-Positive Breast Cancer Versus Healthy Women: A Prospective Case-Control Study. Research Square. 2022.
21. Plaza DJ, Álvarez M, Ruiz-Marín CM, et al. Association of breast and gut microbiota dysbiosis and the risk of breast cancer: a case-control clinical study. BMC Cancer. 2019;19(1):495.
22. Wu AH, Tseng C, Vigen C, et al. Gut microbiome associations with breast cancer risk factors and tumor characteristics: a pilot study. Breast Cancer Res Treat. 2020 Jul;182(2):451–463.
23. Pellegrini M, Ippolito M, Monge T, et al. Gut microbiota composition after diet and probiotics in overweight breast cancer survivors: a randomized open-label pilot intervention trial. Nutrition. 2020;74:110749.
24. Sári Z, Mikó E, Kovács T, et al. Indolepropionic Acid, a Metabolite of the Microbiome, Has Cytostatic Properties in Breast Cancer by Activating AHR and PXR Receptors and Inducing Oxidative Stress. Cancers (Basel). 2020;12(9):2411.
25. Zengul AG, Demark-Wahnefried W, Barnes S, et al. Associations between Dietary Fiber, the Fecal Microbiota and Estrogen Metabolism in Postmenopausal Women with Breast Cancer. Nutr Cancer. 2021;73(7):1108–1117.
26. Shi J, Geng C, Sang M, et al. Effect of gastrointestinal microbiome and its diversity on the expression of tumor-infiltrating lymphocytes in breast cancer. Oncol Lett. 2019;17(6):5050–5056.
27. Giallourou N, Urbaniak C, Puebla-Barragan S, et al. Characterizing the breast cancer lipidome and its interaction with the tissue microbiota. Commun Biol. 2021 Oct 27;4(1):1229.
28. Aarnoutse R, Hillege LE, Ziemons J, et al. Intestinal Microbiota in Postmenopausal Breast Cancer Patients and Controls. Cancers (Basel). 2021;13(24):6200.

rom_Faecal_Specimen_and_Cancerous_Breast_Tissue_A_Co...

ORIGINALITY REPORT

19%	19%	0%	0%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	indonesianjournalofcancer.or.id Internet Source	19%

Exclude quotes	On	Exclude matches	< 5%
Exclude bibliography	On		