·论　著·

乳腺癌患者肿瘤组织及肠道中失调菌群的系统分析

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摘要：目的　通过文献检索的方式找出在乳腺癌患者的肠道或肿瘤组织中富集且与乳腺癌的发生发展密切相关的菌群。**方法**　采用自由词与主题词检索相结合的方式，根据设定的纳入标准、排除标准，从PubMed、Web of Science、Embase、中国生物医学文献数据库、中国知网、万方数据知识服务平台和维普数据库中检索。检索时间从各数据库建库至2022年3月。依次通过浏览标题、摘要和全文进行文献筛选。**结果**　共检索出文献1 110篇，纳入30篇，其中16篇文献描述乳腺癌患者乳腺肿瘤组织相对富集菌群，14篇文献描述乳腺癌患者肠道相对富集菌群。与对照组相比较，乳腺癌患者肠道及肿瘤组织中共同富集的菌群有*Bacteroides*、*Lactobacillus*和*Escherichia coli*。**结论**　乳腺癌患者肠道及肿瘤组织中富集的多种菌群与乳腺癌的发生发展密切相关，肠道及乳腺癌组织中共同富集的*Bacteroides*、*Lactobacillus*和*Escherichia coli*可能与乳腺癌关系最密切，值得深入研究。

关键词：乳腺癌；肠道菌群；肿瘤组织菌群

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Systematic analysis of disordered microbiota in tumor tissues and intestine of breast cancer patients

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Abstract: Objective　To explore the microbiota enriched in the intestinal or tumor tissues of breast cancer (BC) patients and closely related to the occurrence and development of BC through literature search. **Methods**　According to the set inclusion and exclusion criteria, a combination of free word and subject word search was used to search the databases PubMed, Web of Science, Embase, China Biomedical Literature Database, China National Knowledge Infrastructure, Wan-Fang Data Knowledge Service Platform and VIP. The retrieval period was from the establishment of each database to March 2022. Literature selection was carried out by browsing title, abstract and full text successively. **Results**　A total of 1,110 literatures were retrieved and 30 literatures were included. Among them, 16 literatures described the relative enrichment of microflora in breast tumor tissues of BC patients, and 14 literatures described the relative enrichment of microbiota in intestine of BC patients. Compared with the control group, the intestinal and tumor tissues of BC patients enriched *Bacteroides*, *Lactobacillus* and *Escherichia coli*. **Conclusion**　A variety of bacteria enriched in the gut and cancer tissues of BC patients are closely related to the occurrence and development of BC. The enrichment of *Bacteroides*, *Lactobacillus* and *Escherichia coli* in tumor tissues and intestine of BC patients is most closely related to BC, which is worth further study.

Keywords: Breast cancer; Intestinal microbiota; Breast tumor tissue microbiota

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据 GLOBOCAN 在线数据库统计，乳腺癌已成为全球女性最常见的恶性肿瘤，且其发病率及病死率迅速增加，给个人及社会带来了沉重的负担[1]。乳腺癌的发生发展与多种因素密切相关，但是目前对于乳腺癌的确切发病机制尚未明确。随着基因测序技术的不断进步，研究人员发现乳腺癌患者乳腺肿瘤组织及肠道中存在大量细菌，且发现某些特异菌群与乳腺癌的发生发展和预后转归均密切相关[2-4]。然而目前由于研究的异质性，导致各项研究结果存在分歧，与乳腺癌发生发展关系最密切的特异菌群尚未得知。因此本研究通过文献检索的方式对公开发表的关于乳腺癌患者乳腺肿瘤组织及肠道富集菌群的研究进行分析，找出与乳腺癌发生发展密切相关的菌群。通过寻找与乳腺癌关系最密切的细菌，以期从菌群的角度，为靶向菌群诊疗及预防乳腺癌提供新思路和新策略。

1 材料与方法

1.1 检索策略 采用自由词与主题词检索相结合的方式，在线检索 PubMed、Web of Science、Embase、中国生物医学文献数据库（SinoMed）、中国知网（CNKI）、万方数据知识服务平台（WanFang）和维普数据库（VIP），检索时间从各数据库建库至 2022 年 3 月。英文检索词包括“Breast cancer”“Breast tumor”“Breast carcinoma”“Microbiota”“Bacteria”“Microbiome”“Microbiological”“Microbiomes”“Microbial”“Metagenome”，中文检索词包括“乳腺癌”“乳癌”“乳腺肿瘤”“细菌”“菌群”“菌落”“微生物”“微生物群”。

1.2 文献纳入标准与排除标准 纳入标准：（1）研究对象包括乳腺癌患者；（2）研究内容包括乳腺癌患者肠道或乳腺肿瘤组织菌群；（3）研究设计明确，分为病例组与对照组，病例组为乳腺癌患者乳腺肿瘤组织或肠道，对照组为癌旁组织及健康妇女和乳腺良性肿瘤妇女的乳腺组织或肠道；（4）病例组中乳腺癌诊断明确，且以病理结果为诊断的“金标准”。排除标准：（1）非人体相关研究；（2）样本例数少于 10 例，低质量文献；（3）除乳腺组织及肠道外，乳腺癌患者其他部位定植菌群；（4）联系原文作者未回应或不能提供可供分析数据的研究；（5）中、英文以外其他语种写作的文献；（6）综述、会议摘要、讲座、病例报告、专家意见和评论等；（7）重复发表的数据；（8）文献报道信息量太少，缺乏相关资料。

1.3 文献筛选及数据提取 由 2 名研究者独立检索、提取并筛选文献，之后相互核对，对存在分歧的文献提供给第 3 位研究者分析决定是否纳入。提取的数据包括样本量、实验方法以及试验组、对照组中乳腺组织和肠道相对富集菌群。

2 结 果

2.1 文献筛选 共检索出文献 1 110 篇，其中英文文献 714 篇，中文文献 396 篇。通过阅读标题及摘要共剔除 1 029 篇，剔重后获得文献 47 篇，阅读全文后最终纳入 30 篇文献（图 1）。研究对象分别来自中国[5-6]、美国[7-8]、加纳[9]、韩国[10]、英国[11] 及加拿大[11] 等国

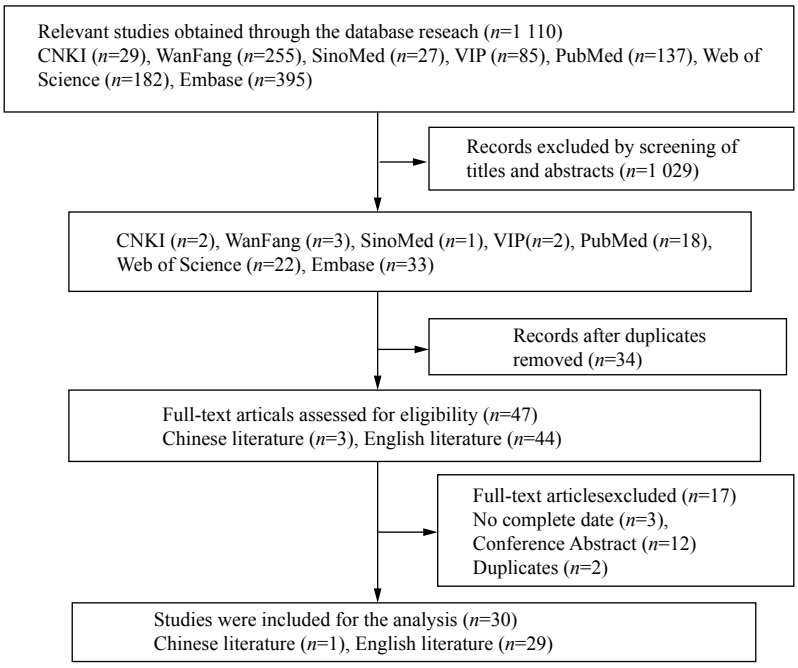

图 1 文献筛选流程

家。实验方法采取 16S rRNA 基因测序、qPCR 及细菌培养等。纳入研究文献的基本特征见表 1、表 2 所示。

表 1　描述乳腺组织相对富集菌群文献的基本特征

文献	样本	方法	相对富集菌群	
			试验组	对照组
[3]	malignant breast cancer（n = 14）, benign breast cancer（n = 9）, NAF-breast cancer survivors（n = 16）, NAF-controls（n = 21）	RT-PCR, immunofluorescence, 16S rRNA gene sequencing	Species: *Bacteroides fragilis*	
[7]	healthy women（n = 40）, breast tumor（n = 61）tissues（samples from African American（n = 27）and non-Hispanic white women（n = 34）	16S rRNA gene sequencing	Family: Enterobacteriaceae,Bifidobacteriaceae Genus: *Bacteroides*, *Streptococcus*	
[10]	47 patients（47 adjacent normal, 47 tumor, 47 lymph node tissues）	16S rRNA Gene Sequencing, qPCR	NO difference	
[11]	43 Canadian women（11 with benign tumors, 27 cancerous tumors and 5 healthy individuals）and 38 Irish women（33 women with BC and 5 healthy individuals）	V6 16S rRNA sequencing（Ion Torrent）, culture,	Species: *Escherichia coli*	
[12]	668 breast tumor tissues and 72 non-cancerous adjacent tissues	V3～V5 16S rRNA amplified sequencing	Phylum: Proteobacteria	Phylum: Actinobacteria
[13]	39 breast cancer（17 tumor, 22 adjacent normal）and 24 healthy women	V3～V4 16S rRNA sequencing（Illumina） Pipeline: UCLUST	Family: Alcaligenaceae	Genus: *Methylobacterium*
[14]	NAF-breast cancer（BC）（n = 6）, NAF-healthy control women（HC）（n = 9）	16S rRNA gene amplicon sequencing	Genus: *Alistipes*	Genus: an unclassified genus from the family Sphingomonadaceae
[15]	tumor and adjacent normal breast tissues（NAT）from 6 TNBC（Triple Negative Breast cancer）WNH（White non-Hispanic）and 7 TNBC BNH（Black non-Hispanic）, 7 TPBC（Triple Positive Breast Cancer）WNH and 3 TPBC BNH patients	16S rRNA gene-based sequencing	TNBC WNH patients, Phylum: Bacteroidetes TPBC patients: Phylum level Fusobacteria Genus: *Streptococcus*	TNBC BNH patients normal tissue: phylum: Actinobacteria and unclassified genus of unclassified Bradyrhizobiaceae
[16]	breast cancer（n = 130）， women with benign breast Lesions（n = 20）	bacterial culture	Species: *Escherichia coli*, *Staphylococcus aureus*	
[17]	221 patients with breast cancer, 87 patients without breast cancer（18 individuals predisposed to breast cancer, and 69 controls）.	16S rRNA gene sequencing,（DADA2-based pipeline）	Family: Pseudomonadaceae, Enterobacteriaceae Genus: *Azomonas*, *Porphyromonas*, *Proteus*, *Pseudomonas*	Genus: *Propionibacterium*, *Staphylococcus*, *Stenotrophomonas*, *Caulobacter*
[18]	paired normal adjacent tissue and tumor tissue from 20 patients with estrogen receptor（ER）-positive breast cancer	16S pyrosequencing, qPCR	Species: *Methylobacterium radiotolerans*	Species: *Sphingomonas yanoikuyae*
[19]	Bilateral normal breast tissue samples（n = 36）were collected from ten women who received routine mammoplasty procedures. Archived breast tumor samples（n = 10）were obtained from a biorepository	16S rRNA sequencing（QIIME）	Family: Ruminococcaceae Genus: *Akkermanisia*	Genus: *Bacteroides*, *Sutterella*
[20]	Benign（n = 22）and malignant（n = 72）breast cancer patients	16S V1～V2 rRNA sequencing（QIIME）	Family: Caulobacteraceae, Methylobacteriaceae, Micrococcaceae, Nocardioidaceae, Rhodobacteraceae Genus: *Propionicimonas*	
[21]	13 benign breast disease and 15 invasive BC（100% ER/PR^{+} and 29% HER^{2+}）	V3～V5 16S rDNA hypervariable taq sequencing（Illumina MiSeq） Pipeline: IM-TORNADO	Genus: *Atopobium, Fusobacterium, Gluconacetobacter, Hydrogenophaga, Lactobacillus*	
[22]	23 Slovakia women（18 cancerous tumors and 5 healthy individuals）and 90 chinese women（72 women with BC and 18 healthy individuals）	16S rRNA gene sequencing	Order: Corynebacteriales Genus: *Acinetobacter, Micrococcus, Rhodobacter, Streptomyces* Species: *Priestia megaterium*	Genus: *Bacteroides, Bifidobacterium, Collinsella, Methylobacterium, Peanibacillus, Pantoea, Sphingomonas, Hymenobacter*
[23]	34 BC patients and the adjacent non-tumoral tissue of each patient	16S Metagenomic Sequencing	Phylum: Firmicutes Class: Alphaproteobacteria	Phylum: Actinobacteria Genus: *Propionibacterium* Species: *Cutibacterium acnes*

表 2 描述肠道相对富集菌群文献的基本特征

文献	样本	方法	相对富集菌群	
			试验组	对照组
[5]	premenopausal breast cancer patients（*n* = 18）, premenopausal healthy control（*n* = 25）, postmenopausal breast cancer patients（*n* = 44）, postmenopausal healthy control（*n* = 46）	Illumina sequencing and taxonomy	not differ significantly between premenopausal breast cancer patients and premenopausal controls. postmenopausal patients; Species: *Escherichia coli, Klebsiella* sp_1_1_55, *Prevotella amnii*, *Enterococcus gallinarum, Actinomyces* sp. HPA0247, *Shewanella putrefaciens*, *Erwinia amylovora*	Species: *Eubacterium eligens, Lactobacillus vaginalis*
[6]	83 patients with invasive breast cancer and 19 patients with benign breast tumors	Illumina sequencing and the taxonomy of 16S rRNA genes	Genus: *Citrobacter*	Family: Erysipelotrichaceae Genus: *Arcanobacterium, Clostridium, Faecalibacterium, Fusicatenibacter, Lachnospira, Romboutsia, Xylophilus*
[8]	48 postmenopausal breast cancer cases（75% stage 0-1, 88% oestrogen-receptor positive）and 48 contemporaneous, postmenopausal, normal-mammogram, age-matched controls	16S rRNA gene amplicon sequencing	Genus: *Parasutterella* Species: *Parasutterella excrementihominis*	Genus: *Oscillibacter, Ruminococcus* Species: *Alistipes indistinctus*
[9]	*n* = 379 breast cancer cases, *n* = 102 non-malignant breast disease cases, *n* = 414 population-based controls	V4 region of the 16S rRNA gene amplicon sequencing	Genus: *Bacteroides, Faecalibacterium*	Genus: *Coprococcus, Romboutsia*,
[24]	20 BC patients, 25 healthy women controls	V3～V6 16S rRNA sequencing	Phylum: Actinobacteria, Firmicutes Genus: *Actinomyces, Aerococcus, Bacillus, Cyanobacterium, Faecalibacterium, Lactococcus, Paenibacillus*	Phylum: Bacteroidetes Genus: *Bacteroides*
[25]	25 breast cancer patients and 25 patients with benign breast disease as controls	16S rDNA sequencing	Phylum: Actinobacteria, Proteobacteria, Verrucomicrobia	Phylum: Bacteroidetes, Firmicutes Genus: *Faecalibacterium*
[26]	54 newly diagnosed premenopausal women with breast cancer（BC）and 28 normal premenopausal women as control group（NC）	16S rRNA gene sequencing	Phylum: Synergistetes Genus: *Butyricicoccus, Clostridium, Desulfovibrio, Eubacterium, Intestinibacter,Providencia, Romboutsia,Terrisporobacter, Turicibacter*	Phylum: Acidobacteria, Cyanobacteria, Fusobacteria, Nitrospirae Genus: *Enhydrobacter, Fusobacterium, Pediococcus*
[27]	267 breast cancer patients with different menopausal statuses and age-matched female controls（Pre-C *n* = 50, Pre-BC *n* = 100, Post-C *n* = 17, Pre-BC *n* = 100）	V3～V4 16S rRNA sequencing	Genus: *Sutterella, Haemophilus*	Genus: *Akkermansia, Bifidobacterium*
[28]	30 healthy women controls, 25 BC patients	V3～V4 16S rRNA gene sequencing	Phylum: Firmicutes Genus: *Blautia*	Phylum: Bacteroidetes Species: *Butyricimonas* sp., *Coprococcus* sp., *Odoribacter* sp.
[29]	14 healthy women controls, 14 BC patients	V4 16S rRNA sequencing（QIIME）	Family: Lachnospiraceae, Ruminococcaceae, Tissierellaceae	Class：Alphaproteobacteria Family: Veillonellaceae Genus: *Aquabacterium, Vogesella*
[30]	81 postmenopausal $ER^+/HER2^-$ breast cancer patients and 67 postmenopausal controls	V4 16S rRNA sequencing	No difference	
[31]	48 postmenopausal breast cancer case patients, pretreatment and 48 control patients	Illumina sequencing	Family: Clostridiaceae, Ruminococcaceae Genus: *Faecalibacterium*	Family: Lachnospiraceae Genus: *Dorea*
[32]	18 patients with breast cancer and 30 healthy women	After incubation different colony types were enumberated, isolated, and identified by Gram-stain, morphological, and biochemical	Class: Clostridia Genus: *Lactobacillus, bacteroides* Species: *Escherichia coli*	
[33]	23 women with breast cancer and 23 healthy women	16S rRNA amplification and Illumina sequencing	Genus: *Bifidobacterium, Blautia, Eubacterium*	Genus: *Anaerostipes, Faecalibacterium, Parabacteroides, Phascolarctobacterium*

2.2　文献汇总分析

2.2.1　乳腺癌患者乳腺肿瘤组织内存在菌群失调　研究发现，与健康妇女乳腺组织、乳腺良性肿瘤患者的乳腺肿瘤组织以及乳腺癌癌旁组织相比，乳腺癌患者肿瘤组织内菌群组成及丰度存在差异。纳入的 16 篇文献通过 16S rRNA 基因测序、细菌培养、PCR 等方法对比发现，乳腺癌患者的乳腺肿瘤组织微环境中存在菌群失调。与对照组相比，在菌门水平上，乳腺癌患者肿瘤组织中 Alcaligenaceae、Bifidobacteriaceae、Caulobacteraceae、Enterobacteriaceae、Methylobacteriaceae、Micrococcaceae、Nocardioidaceae、Pseudomonadaceae、Ruminococcaceae 和 Rhodobacteraceae 丰度较高[7,13,17,19-20]；在菌属水平上，乳腺癌患者肿瘤组织中 *Acinetobacter*、*Alistipes*、*Azomonas*、*Atopobium*、*Akkermanisa*、*Bacteroides*、*Fusobacterium*、*Gluconacetobacter*、*Hydrogenophaga*、*Lactobacillus*、*Micrococcus*、*Proteus*、*Porphyromonas*、*Pseudomonas*、*Propionicimonas*、*Rhodobacter*、*Streptococcus* 和 *Streptomyces* 丰度较高[7,14-15,17,19-22]；在菌种水平上，乳腺癌患者肿瘤组织中 *Bacteroides fragilis*、*Escherichia coli*、*Staphylococcus aureus*、*Methylobacterium radiotolerans* 和 *Priestia megaterium* 丰度较高[3,11,16,18,22]。

2.2.2　乳腺癌患者肠道内存在菌群失调　随着基因测序技术的发展，对乳腺癌患者的肠道菌群研究愈发增多。多名研究者发现，与健康妇女或乳腺良性肿瘤患者肠道微生物相比较，乳腺癌患者肠道内菌群组成及丰度存在差异。纳入的 14 篇文献通过 16S rRNA 基因测序、菌群培养及染色等方法，与对照组相比，在菌科水平上，乳腺癌患者肠道中 Clostridiaceae、Lachnospiraceae、Ruminococcaceae 和 Tissierellaceae 丰度较高[29,31]；在菌属水平上，乳腺癌患者肠道中 *Actinomyces*、*Aerococcus*、*Bacteroides*、*Bacillus*、*Blautia*、*Bifidobacterium*、*Butyricicoccus*、*Citrobacter*、*Clostridium*、*Cyanobacterium*、*Desulfovibrio*、*Eubacterium*、*Faecalibacterium*、*Haemophilus*、*Intestinibacter*、*Lactococcus*、*Lactobacillus*、*Parasutterella*、*Paenibacillus*、*Providencia*、*Romboutsia*、*Sutterella*、*Terrisporobacter* 和 *Turicibacter* 丰度较高[6,8-9,24,26-28,31-33]；在菌种水平上，乳腺癌患者肠道中 *Actinomyces* sp. HPA0247、*Escherichia coli*、*Enterococcus gallinarum*、*Erwinia amylovora*、*Klebsiella* sp_1_1_55、*Parasutterella excrementihominis*、*Prevotella amnii* 和 *Shewanella putrefaciens* 丰度较高[5,8,32]。

2.2.3　乳腺癌患者肿瘤组织及肠道中存在相同富集菌群　纳入的 30 篇文献提示了乳腺癌患者肿瘤组织及肠道中富含相同菌属，如 *Bacteroides*、*Lactobacillus*。与对照组相比，乳腺癌患者乳腺肿瘤组织及肠道中富集菌属如图 2 所示。

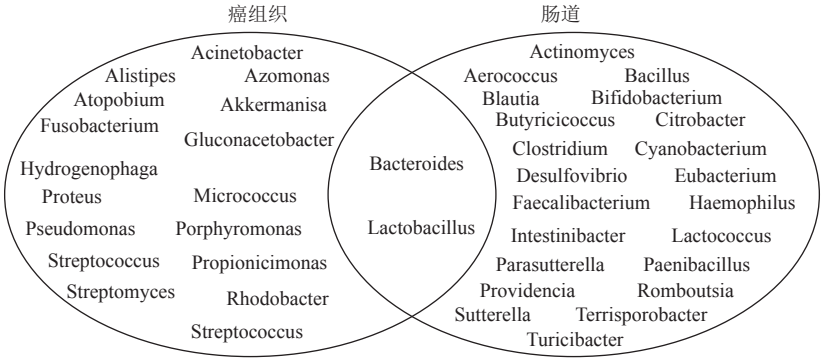

图 2　乳腺癌患者癌组织及肠道中上调菌属

纳入的 30 篇文献提示了乳腺癌患者肿瘤组织及肠道中富含相同上调菌种，如 *Escherichia coli*。与对照组相比，乳腺癌患者乳腺肿瘤组织及肠道中富集菌种如图 3 所示。

3　讨　论

3.1　研究结果分析　乳腺癌患者乳腺肿瘤组织及肠道内富集菌群可能与乳腺癌的发生发展密切相关。在乳腺肿瘤组织中富集的 *Bacteroides fragilis* 可分泌脆弱拟杆菌毒素，通过 β-catenin 和 Notch1 轴诱导乳腺导管内肿瘤细胞浸润转移[3]。乳腺癌患者肠道中富集的 *Clostridium*、*Bacteroides*、*Bifidobacterium*、*Escherichia*、*Faecalibacterium*、*Klebsiella*、*Enterobacter* 和 *Citrobacter* 能编码葡萄糖醛酸酶[34-36]。葡萄糖醛酸酶可加快雌激素的羟基化和早期解离，升高血液中游离雌激素水平，使其随血液循环至乳腺等靶器官。乳腺癌的发生与高雌激素水平及代谢相关，尤其在绝经后的女性中。此外研究发现，雌激素不仅能够

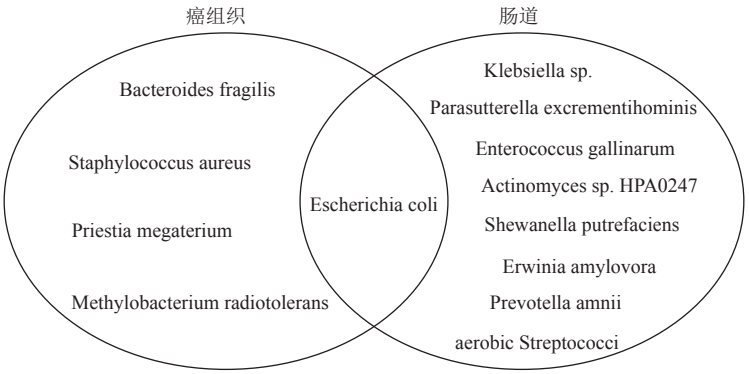

图 3 乳腺癌患者癌组织及肠道中上调菌种

促进乳腺正常上皮细胞和癌细胞增殖[37]，还能通过 Notch 信号通路促进乳腺癌转移[38]。研究者在体外培养的乳腺癌细胞中发现，*Streptococcus mitis* 产生的活性刺激肽、*Bacillus subtilis* 产生的 PhrG、*Escherichia coli* 产生的细胞外坏死因子（extracellular death factor，EDF）及其类似物可通过 I 型胶原细胞外基质途径促进乳腺癌细胞浸润及血管形成，诱导乳腺癌细胞转移[39]。其中，*Streptococcus mitis* 属于 *Streptococcus* 属，在乳腺癌患者的癌组织中富集；*Bacillus subtilis* 属于 *Bacillus* 属，在乳腺癌患者的肠道中富集。*Actinomyces* sp. HPA0247 和 *Fusobacterium nucleatum* 可抑制乳腺癌组织中浸润性 T 淋巴细胞的积聚，从而促进乳腺肿瘤生长和转移进展[2,5]。研究还发现 *Fusobacterium nucleatum* 可能通过激活 Toll 样受体 4 途径和抑制免疫系统来促进乳腺癌的进展，通过自噬和免疫逃避导致肿瘤细胞生长和治疗抵抗[40]。其中，*Actinomyces* sp. HPA0247 属于 *Actinomyces* 属，在乳腺癌患者的肠道中富集，*Fusobacterium nucleatum* 属于 *Fusobacterium* 属，在乳腺癌患者的癌组织中富集。与健康妇女乳腺组织相比，乳腺癌患者癌组织内富集 *Escherichia coli*，进一步对 *Escherichia coli* 菌群进行分离、研究，发现其在体外实验中可直接导致 HaLa 细胞 DNA 双链断裂[41]，而 DNA 双链断裂与肿瘤发生密切相关。*Escherichia coli* 在乳腺癌患者的肠道及癌组织中的丰度均上调。

乳腺癌患者肠道及乳腺组织富集菌群也有可能为有益菌群。*Faecalibacterium prausnitzii* 是 *Faecalibacterium* 属中最常见的菌种，可抑制乳腺肿瘤微环境中 IL-6 的产生及 JAK2 和 STAT3 的磷酸化，从而抑制乳腺癌细胞的增殖和侵袭，促进癌细胞凋亡[25]。*Faecalibacterium* 属在乳腺癌患者的肠道中富集。此外，研究发现，口服益生菌 *Lactobacillus acidophilus* 能使患有乳腺癌的小鼠产生 Th1 型免疫反应，使 IL-4、TGF-β 产生减少，IFN-γ 产生增加，增加 NK 细胞活性，有利于抗肿瘤免疫，降低乳腺肿瘤的生长速率[42]。给予由益生菌 *Lactobacillus casei* 发酵的牛奶，可对乳腺癌小鼠发挥免疫调节作用，降低血清中 IL-10、IL-6 水平，使 IL-10/IL-6 比值升高、IgA^+细胞显著增加，延缓乳腺肿瘤的发展[43]。目前 *Lactobacillus acidophilus* 已被证实对人类乳腺癌细胞具有良好的抗肿瘤能力[44]。益生菌 *Lactobacillus acidophilus*、*Lactobacillus casei* 均属于 *Lactobacillus* 属。*Lactobacillus* 属在乳腺癌患者肠道及肿瘤组织中均富集。

3.2 研究意义 本研究首次对乳腺癌与菌群失调进行了系统分析，通过文献检索的方式分析与乳腺癌关系密切的相关菌群。综上所述，乳腺癌患者肠道及癌组织中富集的菌群与乳腺癌的发生发展密切相关，其可能为有害菌群也有可能为有益菌群，肠道及乳腺癌组织中共同富集的 *Bacteroides*、*Lactobacillus* 和 *Escherichia coli* 可能与乳腺癌关系最密切，有必要通过高质量、大样本、多中心的研究，为今后深入的机制研究或临床转化提供更多的循证医学证据。

3.3 不足之处 本研究结果提示乳腺癌患者的肠道及乳腺组织内存在菌群失调，且失调菌群可能在乳腺癌的发生发展过程中起着主要作用。但同时，本研究也存在局限性：（1）微生物群的个体间异质性、方法学的差异（DNA 提取试剂盒、测序的目标可变区选择、组织提取和储存）以及患者特征（种族、饮食习惯、绝经状态、乳腺癌亚型、分期等）限制了结果的可比性；（2）纳入的研究样本量仍然较小，需要更多大样本多中心的研究；（3）本研究无法确定肠道及乳腺肿瘤组织中失调菌群与乳腺癌之间的“因果关系”；（4）由于乳腺肿瘤样本中菌群生物量较低及污染等原因可能会导致结果不准确；（5）研究表明乳腺癌患者尿液中也存在菌群失调[13]，本研究只纳入了乳腺组织及肠道菌群的文献，而未纳入其他部位（如口腔、血液、尿液及阴道等）菌群的文献，可为今后的研究方向提供新思路。

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