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微生物群在乳腺癌中的研究进展

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摘 要

乳腺癌是女性癌症相关死亡的重要原因且病因不明，少数与遗传易感性有关，多数为散发，散发性病例的病因是癌症研究的一个重要领域。越来越多的研究显示微生物群失调与乳腺癌发生发展相关，本文对乳腺癌患者乳腺皮肤、乳腺组织、乳汁和肠道中发现的微生物及其对治疗的影响进行综述，对乳腺癌与微生物群的关系进行初步探索。

关键词

微生物群，乳腺癌，诊断，治疗

Research Progress of Microbiome in Breast Cancer

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Abstract

Breast cancer is a significant cause of cancer-related death in women and its etiology is unknown. A small number of patients are associated with genetic susceptibility and most are disseminated. The cause of sporadic cases is an important area of cancer research. A growing number of studies have shown that microbiota dysbiosis is associated with the development of breast cancer. This article provides a review of the microbiota found in the breast skin, breast tissue, milk and intestine of breast cancer patients and its impact on treatment, with the aim of providing a preliminary

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exploration of the relationship between breast cancer and the microbiota.

Keywords

Microbiota, Breast Cancer, Diagnosis, Treatment

1. 引言

乳腺癌是女性中最常见的癌症。尽管在过去的几十年里，由于在检测和治疗方面的进步，其死亡率稳步下降，但大多数乳腺癌病例的病因仍然未知。虽然乳腺癌与 BRCA1/2 基因突变等遗传风险因素和久坐的生活方式、肥胖、酒精、激素替代疗法等环境风险因素有关，但是，在罕见的基因突变和环境暴露的条件下，只有少数人才会发展为癌症，多数散发病例的发病风险基本相同，这表明还可能存在其他不确定的风险因素[1]。在过去的几十年里，人体微生物群在包括癌症在内的多种疾病中引起了广泛的关注，人类宿主与微生物群之间存在着一种动态而复杂的关系，研究显示微生物失调在慢性炎症、细胞癌变和免疫逃避中发挥重要作用，幽门螺杆菌(*Fusobacterium*)在胃癌和结直肠癌中的作用已被报道[2] [3]。虽然尚未证明微生物失调可导致乳腺癌，但是研究显示乳腺癌患者和健康个体之间某些特定细菌类群的组成和丰度确实存在差别，并可能与治疗效果的个体差异有关[4] [5]。目前关于微生物群与乳腺癌研究相对较少，且人体不同部位的微生物组成差异明显，它们如何影响乳腺癌的发生发展及治疗，仍需进一步探索，因此本文对乳腺癌患者乳腺皮肤、乳腺组织、乳汁和肠道中发现的微生物及其对治疗的影响进行综述，探索微生物群与乳腺癌的关系。

2. 乳腺癌患者的乳腺微生物群变化

2.1. 乳腺皮肤微生物群变化

研究表明，与乳腺组织内微生物群相比，乳腺皮肤的微生物群多样性更高，且乳腺癌患者乳腺皮肤表面拟杆菌门(*Bacteroidetes*)、丛毛单孢菌科(*Comamonadaceae*)、肠杆菌科(*Enterobacteriaceae*)、甲基杆菌属(*Methylobacterium*)、梭杆菌属(*Fusobacterium*)、*Brevundimonas* 属、*Atopobium* 属和 *Gluconacetobacter* 属丰度升高，这些微生物群可能会从皮肤表面转移到乳腺组织内，破坏乳腺组织内微生物群平衡[6] [7]。乳腺癌患者乳腺皮肤表面的葡萄球菌属(*Staphylococcus*)可能与乳腺癌的远处转移有关[8]。

2.2. 乳腺组织微生物群变化

乳房组织曾经被认为是无菌的，后来发现其具有多样且独特的微生物群组成[7]。通过对乳腺癌组织及距离癌灶边缘约 5 厘米的癌旁组织微生物群进行检测，研究者发现乳腺癌组织中细菌丰度及多样性更高[9]。在门水平上，乳腺癌组织中变形菌门(*Proteobacteria*)丰度最高，而癌旁组织中放线菌门(*Actinobacteria*)丰度最高[10]；在纲水平，乳腺癌组织中梭菌纲(*Clostridia*)和拟杆菌纲(*Bacteroidia*)丰度最高；在科水平，乳腺癌组织中假单胞菌科(*Pseudomonadaceae*)、鞘脂单胞菌科(*Sphingomonadaceae*)、产碱杆菌科(*Alcaligenaceae*)以及瘤胃球菌科(*Ruminococcaceae*)科丰度升高[11] [12]；在属水平，乳腺癌组织中甲基杆菌属(*Methylobacterium*)丰度最高，其次为鞘氨醇单胞菌属(*Sphingomonas*)和 *Ralstonia* 属[11] [12]。

与正常乳腺组织相比，乳腺癌癌旁组织中拟杆菌门(*Bacteroidetes*)、*β* 变形杆菌科(*Comamondaceae*)、肠杆菌科(*Enterobacteriaceae*)、芽孢杆菌属(*Bacillus*)、葡萄球菌属(*Staphylococcus*)以及大肠埃希氏杆菌(*Escherichia coli*)丰度升高[13]。从癌旁组织分离、培养的大肠埃希氏杆菌(*Escherichia coli*)可在体外诱导宫颈癌细胞 DNA 双链断裂[13]。此外，含有 pks 基因簇的基因毒性大肠杆菌(pks^+ *Escherichia coli*)产生的具有遗传毒性的代谢物 *Colibactin* 可导致肠道细胞 DNA 损伤，这可能与乳腺癌发生有关[14]。这些研究表明正常乳腺组织、癌旁组织以及乳腺癌组织的微生物群组成差异明显，乳腺组织微生物群可能在乳腺癌发生发展过程中发生改变，了解这种改变对评估乳腺癌发展及预后非常重要。

不同分期的乳腺癌微生物组成存在差异，在 I 期乳腺癌中，变形菌门(*Proteobacteria*)、瘤胃球菌科(*Ruminococcaceae*)以及 *Hyphomicrobium* 属为优势微生物群；在 II 期乳腺癌中，广古菌门(*Euryarchaeota*)、厚壁菌门(*Firmicutes*)、螺旋体门(*Spirochaetes*)以及 *Sporosarcina* 属为优势微生物群[12]；在 III 期及 IV 期乳腺癌中，芽单胞菌门(*Gemmatimonadetes*)、软壁菌门(*Tenericutes*)及 *Bosea* 属为优势微生物群；*Agrococcus* 属丰度随着乳腺癌分期升高而增加[15]。此外，不同分子分型的乳腺癌微生物群组成也存在差异。在 Luminal A 型乳腺癌组织中，*Xanthomonadales* 目丰度最高；在 Luminal B 型乳腺癌组织中，*Clostridium* 属丰度最高[12]，且与正常乳腺组织相比，大多数激素受体阳性型乳腺癌组织中 *Methylobacterium* 属丰度下降[11]；在 Her2 阳性乳腺癌组织中，艾克曼菌属(*Akkermansia*)丰度最高；在三阴性乳腺癌组织中，链球菌科(*Streptococcaceae*)和瘤胃球菌属(*Ruminococcus*)丰度最高[12]。乳腺癌与乳腺良性结节微生物群组成也有差异，与乳腺良性结节相比，乳腺癌组织中变形菌门(*Proteobacteria*)、微球菌科(*Micrococcaceae*)、柄杆菌科(*Caulobacteraceae*)、*Rhodobacteraceae* 科、甲基杆菌科(*Methylobacteriaceae*)、*Nocordioidaceae* 科以及 *Propionicimonas* 属丰度明显升高[15]。这表明不同分期及不同分子分型的乳腺癌组织微生物群组成差异巨大，探索乳腺癌组织的微生物群差异可能有助于其临床诊断。

2.3. 乳汁微生物群变化

乳汁中的微生物群主要由胃肠道微生物群通过肠－乳腺轴转移到乳汁，也可以在母乳喂养期间通过婴儿的口腔转移到乳汁。妊娠、分娩、哺乳、饮食和抗生素均会影响乳汁中微生物群组成。厚壁菌门(*Firmicutes*)、放线菌门(*Actinobacteria*)和拟杆菌门(*Bacteroidetes*)是乳汁中的优势菌门[16]，葡萄球菌属(*Staphylococcus*)、沙雷氏菌属(*Serratia*)、棒状杆菌属(*Corynebacteria*)和链球菌属(*Streptococcus*)是乳汁中的优势菌属[17]，乳汁中还含有多种双歧杆菌(*Bifidobacterium*) [18]。乳汁中的乳酸杆菌包含丰富的免疫调节 DNA 序列，有助于机体免疫应答，甚至可用于治疗乳腺疾病[19]。与健康女性相比，乳腺癌患者的乳头吸取液中另枝菌属(*Alistipes*)丰度较高，而鞘脂单胞菌科(*Sphingomonadaceae*)中部分菌属丰度较低[20]，这表明乳腺癌患者和健康女性乳头吸取液中的微生物群组成存在显著差异，乳腺导管微生物群在乳腺癌发生中可能发挥潜在作用。

3. 肠道微生物群与乳腺癌

3.1. 乳腺癌患者肠道微生物群变化

与人体的其他器官相比，肠道中微生物群含量最高且组成复杂，肠道微生物群及其代谢物在维持肠道健康中发挥重要作用，可以促进宿主免疫系统的发育，协助肠道从饮食中吸收营养物质并产生维生素及氨基酸[21]。微生物群组成结构的破坏可能会影响宿主的免疫调节和炎症，有利于疾病的发生发展[22]。肠道的微生物群可能在癌症中发挥双重作用，一方面促进恶性肿瘤进展，另一方面特定的微生物群可以促进抗肿瘤免疫。脆弱拟杆菌(*Bacterioides fragilis*)在细胞毒性 T 细胞发挥抗肿瘤作用中扮演重要角色[23]，比菲德氏菌(*Bifidobacteria*)可以提高 PD-1 抑制剂治疗效果[24]，并且肠道微生物群可能降缓解疗相关毒

副反应，提高治疗效果。

部分肠道微生物群的丰度的变化与癌症发生有关。幽门螺杆菌(*Helicobacter pylori*)已被证实可以引起胃癌，梭菌属(*Fusobacterium*)丰度升高与结直肠癌发生有关[25] [26]。目前关于肠道微生物群与乳腺癌相互作用机制未明，大部分研究都停留在探索乳腺癌患者微生物群变化的阶段，其中关于绝经后乳腺癌患者肠道微生物群变化的研究最多。与健康对照绝经后女性相比，绝经后乳腺癌患者肠道微生物群多样性降低，这通常意味着少数致病菌的过度繁殖，相应的，肠道微生物群多样性升高可以促进乳腺癌患者治疗后的心理及心肺健康。绝经后乳腺癌患者肠道内的腐败希瓦氏菌(*Shewanella putrefaciens*)、解淀粉欧文氏菌(*Erwinia amylovora*)、*Roseburia inulinivorans* 菌以及 *Actinomyces sp. HPA0247* 菌丰度升高，梭菌科(*Clostridiaceae*)、瘤胃球菌科(*Ruminococcaceae*)以及 *Faecalibacterium* 属丰度下降，这些微生物群可能与机体雌激素代谢及肿瘤浸润免疫细胞相关[27] [28]。

不同临床分期乳腺癌肠道微生物群组成存在差异。与 I 期乳腺癌相比，II 期及 III 期乳腺癌的微生物群总量降低，乳腺癌临床分期越晚，梭菌属(*Clostridium*)和韦荣氏球菌属(*Veillonella*)丰度越高，丹毒丝菌科(*Erysipelotrichaceae*)丰度越低，肠道中布劳特氏菌属(*Blautia*)及普拉氏梭杆菌(*F. prausnitzii*)比例以及双歧杆菌属(*Bifidobacterium*)丰度也与乳腺癌临床分期相关，这表明微生物群可能参与了乳腺癌的进展[29]。此外，乳腺癌患者的易疲劳、焦虑和心肺健康程度与肠道中普雷沃菌属(*Prevotella*)、拟杆菌属(*Bacteroides*)、粪球菌属(*Coprococcus*)、罗氏菌属(*Roseburia*)以及 *Faecalibacterium* 属丰度有关[30]。这些研究表明肠道微生物群可能作为乳腺癌的标志物或治疗位点，需要更多的研究在功能水平对乳腺癌患者的肠道微生物群进行探索。

3.2. 环境因素对肠道微生物群影响

肠道微生物群在很大程度上受到年龄、饮食、药物及宿主遗传等环境因素的影响，并且处在动态变化中，通常认为稳定且多样的肠道微生物群最有利于人体健康。

饮食对肠道微生物群多样性有着重要影响，改变饮食模式可以影响肠道微生物群，并间接影响乳腺癌的发生[31]。“地中海饮食模式”中蔬菜、水果和鱼类的摄入使乳腺组织中乳杆菌属(*Lactobacillus*)丰度升高，同时肠道内胆汁酸含量增加，乳腺癌患病风险降低[32]。低脂饮食可以降低肿瘤切除术后复发风险[33]，对三阴性乳腺癌小鼠饮食热量限制后，其胰岛素样生长因子及其相关通路发生变化，使乳腺癌远处转移风险降低[34]。与之相反的是，西方饮食模式中的高脂、高糖可能增加患乳腺癌风险[35]。过量饮酒可能损伤乳腺细胞、影响肝脏中与雌激素代谢相关的酶的活性进而增加患乳腺癌风险。研究显示，口服槲皮素可以明显缩小 C3/SV40 Tag 乳腺癌小鼠模型的肿瘤体积，饮食中的葡萄多酚，包括白藜芦醇、儿茶素等可以通过下调 NF-κB 的表达进而抑制小鼠体内原发肿瘤的生长，白皮杉醇可以降低可以抑制巨噬细胞浸润和血管生成，阻止肿瘤远处转移[36] [37]。

抗生素不仅可以影响致病菌，而且可以影响肠道中有益共生菌，其影响程度受抗生素种类、作用方式以及微生物群对抗生素的耐药程度。过度使用抗生素会增加微生物群失调可能性，降低微生物群多样性，并且可能会影响人体雌激素水平，增加患乳腺癌风险[38]，幸运地是，抗生素引起的微生物群失调通常在一段时间后可以自行恢复[39]。显然，饮食中的特定成分及抗生素可能在乳腺癌的发生发展中发挥重要作用，需要进一步研究对其涉及的相关机制，为未来进行治疗干预提供可能。

4. 微生物群对乳腺癌治疗的影响

4.1. 微生物群对化疗的影响

微生物群和癌症之间的相关性为乳腺癌的治疗带来新的角度。体外实验发现益生菌可以抑制粪肠球

菌(*Enterococcus faecalis*)以及人葡萄球菌(*Staphylococcus hominis*)增殖，在小鼠体内的研究发现，口服罗伊氏乳杆菌(*Lactobacillus reuteri*)可以抑制细胞癌变，提高乳腺细胞对凋亡信号的敏感性[40] [41]。微生物群还可以影响癌症患者的化疗效果和预后，三阴性乳腺癌患者的肠道和瘤内微生物群与接受 AC-T 新辅助化疗方案后的病理缓解程度相关，在晚期 Her2 阳性乳腺癌患者中的研究发现，接受卡培他滨治疗后，患者肠道微生物群多样性下降，进一步研究发现 *Blautiaobeum* 属与无病生存期呈正相关($P = 0.013$)，而 *Slackia* 属与无病生存期呈负相关($P = 0.004$) [42] [43]。

微生物群主要通过影响药物代谢和药物毒性来影响化疗效果[44]。大部分化疗药物在进入血液循环系统被机体利用之前需要经过酶对其进行相应的代谢，而肠道微生物群可以产生大量的酶，因此，微生物群组成可以影响治疗效果。目前已知有四十多种药物受微生物群代谢影响[45]。乳腺癌组织中的大肠杆菌(*Escherichia coli*)在体外实验中增强替加氟、磷酸氟达拉滨、5-氟胞嘧啶的细胞毒性，降低阿糖腺苷、吉西他滨、阿霉素的细胞毒性[46]。嗜酸乳杆菌(*Lactobacillus acidophilus*)产生的活性氧通过增强铂类化疗药的 DNA 损伤和断裂效应，协助顺铂在无菌鼠体内发挥抗肿瘤活性，局部和全身的细菌感染可能增强化疗药在靶向区域外的毒性，抗生素破坏微生物群组成并影响铂类化疗药及免疫治疗效果[4] [47]，这些微生物群与药物之间的相互作用使癌症治疗过程变得更加复杂。总的来说，微生物群稳态有利于抗癌药物在体内更好的发挥作用，肠道微生物群组成可能在治疗前对乳腺癌患者化疗药效果进行预测，有助于乳腺癌患者化疗药的选择。

4.2. 微生物群对放疗的影响

放疗是乳腺癌治疗中的另一种重要的治疗方式。放疗可用于保乳术后，抑制癌症局部复发，提高总生存率。关于微生物群与放疗的研究较少。肠道细菌和真菌可以通过影响免疫系统进而影响机体对放疗的敏感性。肿瘤微环境对放疗敏感程度起决定性作用。微生物群代谢物通过调节葡萄糖利用和脂肪酸氧化之间的平衡，影响细胞代谢，进而影响肿瘤微环境的免疫反应以及癌细胞的放疗敏感性[48]。在巨噬细胞极化过程中，细胞代谢发生改变，M1 型巨噬细胞可以增强乳腺癌细胞的放疗敏感性，相反的，M2 型巨噬细胞通过 IL-4 或 IL-13 诱导的 STAT6 磷酸化和 M2 极化来激发放疗抵抗[48] [49]。放射性皮炎是乳腺癌放疗患者最常见的不良反应之一，急性放射性皮炎主要表现为红斑、脱屑和溃疡等，严重者甚至需要中断放疗，慢性放射性皮炎常发生于放疗后的数月至数年间，主要表现为主要表现为皮肤萎缩、色素沉着、迟发性溃疡、皮肤纤维化等，严重影响患者的生活质量，放射性皮炎可能与机体异常炎性反应相关，研究表明金黄色葡萄球菌(*Staphylococcus aureus*)超抗原可以通过激活 T 细胞来阻止表皮修复，进一步加剧放射性皮炎[50]。

4.3. 微生物群对免疫治疗的影响

越来越多的研究表明微生物群可以影响免疫抑制剂的治疗效果。拟杆菌属(*Bacteroides*)中部分菌种，特别是多形拟杆菌(*B. thetaiotaomicron*)和脆弱类杆菌(*B. fragilis*)会影响 CTLA-4 单抗的免疫治疗效果，肠道中丰富的瘤胃球菌科(*Ruminococcaceae*)可以提高黑色素瘤患者的抗 PD-1 治疗效果[51]。在三阴性乳腺癌患者中，双歧杆菌(*Bifdobacterium*)和嗜黏蛋白阿克曼菌(*Akkermansia muciniphila*)可能通过增强抗原呈递，促进肿瘤微环境中 T 细胞募集来增强机体免疫应答，协助 PD-L1 抑制剂在体内发挥效应，并且可以提高肠道微生物群多样性，延长患者的生存期，而乳腺癌患者术中或术后使用的抗生素会降低嗜黏蛋白阿克曼菌(*Akkermansia muciniphila*)丰度，削弱 PD-1 抑制剂的效果，缩短患者的生存期[52] [53]。这些结果表明，微生物群结构的差异可能会帮助患者选择更有针对性的个性化的治疗方案，将肠道微生物群失调状态调整为正常稳态在可能作为乳腺癌的辅助治疗手段，减轻患者免疫治疗耐药程度[54]。

这些研究表明，微生物群可以影响乳腺癌的化疗、放疗以及免疫治疗效果，对微生物群的干预可能会为乳腺癌的治疗打开新视野，但是需要更多的研究对肠道微生物群与治疗手段之间的相互作用机制进行探索。

5. 小结与展望

本文通过对微生物群与乳腺癌的相关研究进行总结，发现主要存在两个关键问题，第一，虽然事实证明乳腺癌患者微生物群与健康对照确实存在差异，然而这些大多数是关联性研究，乳腺癌与微生物群的因果关系并不明确；第二，肠道与乳房微生物群之间是否存在网络或联系，两者是否协同作用形成有利于乳腺癌发生发展的环境，这也有待探索。但是不可否认微生物群在乳腺癌诊断、治疗及预后中有着巨大潜力，并且益生菌等工程菌作为一种非侵入性手段，可能为乳腺癌临床治疗打开新模式。

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