Advances in Clinical Medicine 临床医学进展, 2025, 15(3), 208-217
Published Online March 2025 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2025.153606

Hans汉斯

肠道菌群与乳腺癌及新辅助治疗

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收稿日期：2025年2月5日；录用日期：2025年2月28日；发布日期：2025年3月6日

摘　要

肠道菌群具有调节乳腺癌发生发展并改善治疗的作用，本综述结合了近年来国内外相关研究试验，总结了相关研究进展，分析了肠道菌群通过DNA损伤、类固醇激素、代谢产物、免疫及炎症反应等机制参与乳腺癌的发生发展；详细阐述了肠道菌群对化疗、靶向治疗等新辅助治疗药物的相互作用；简单讨论了益生菌利用其关系在未来为乳腺癌的预防、诊断及治疗提供了新的思路。

关键词

乳腺癌，肠道菌群，新辅助治疗，免疫，炎症反应，化疗，靶向治疗

Gut Microbiota, Breast Cancer, and Neoadjuvant Therapy

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Received: Feb. 5th, 2025; accepted: Feb. 28th, 2025; published: Mar. 6th, 2025

Abstract

The gut microbiota plays a role in regulating the occurrence and development of breast cancer and improving treatment. This review integrates relevant domestic and foreign research trials in recent years, summarizes the related research progress, and analyzes the mechanisms by which the gut microbiota is involved in the occurrence and development of breast cancer, including DNA damage, steroid hormones, metabolites, immune, and inflammatory responses. It elaborates on the interactions between the gut microbiota and neoadjuvant therapeutic drugs such as chemotherapy and targeted therapy. Additionally, it briefly discusses how probiotics, leveraging these relationships,

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文章引用: 夏晨玥, 张国武. 肠道菌群与乳腺癌及新辅助治疗[J]. 临床医学进展, 2025, 15(3): 208-217.
DOI: 10.12677/acm.2025.153606

may provide new perspectives for the prevention, diagnosis, and treatment of breast cancer in the future.

Keywords

Breast Cancer, Intestinal Microbiota, Neoadjuvant Therapy, Immunity, Inflammatory Response, Chemotherapy, Targeted Therapy

1. 引言

根据世界卫生组织最新的数据，乳腺癌已取代肺癌成为全球第一大肿瘤，是世界上最常见的癌症之一[1]。有报告显示，近几十年来，乳腺癌的发病率不断上升[2]，成为影响女性生命健康及生活质量的重要疾病因素。肠道菌群与乳腺癌发生发展的相关性已被大量发掘，近几年的研究更揭示了肠道菌群与乳腺癌化疗乃至靶向治疗之间的紧密联系，肠道菌群能一定程度地促进乳腺癌患者化疗及靶向治疗的疗效，抑制乳腺肿瘤细胞远处转移，降低其进展和复发的风险，并降低化疗不良反应的发生率。基于此理论上，无论是新辅助治疗还是辅助治疗均能从中获益，本文结合近年相关的研究，系统地阐述有关肠道菌群与乳腺癌发病机制的关系以及肠道菌群对新辅助治疗调节的相关研究进展，为肠道菌群参与乳腺癌治疗的调控提供理论依据。

2. 肠道菌群与乳腺癌

在人体中，存在于胃肠道的微生物群落叫肠道微生物群，人类与肠道微生物长期共存，肠道微生物在维持人类的健康中发挥了不可忽视的作用，在与宿主保持动态平衡的同时，局部或远程地参与人体重要的生理过程，特别是炎症和免疫反应[3]。与以往观念不同的是，乳房并非无菌环境，而是由特定的微生物种群及乳腺组织组成[4] [5]，近些年的研究指出肠道菌群可在乳腺癌、肺癌、卵巢癌等非肠道组织中大量存在[6]，这些菌群保证了乳腺功能的正常发挥并共同参与乳腺组织细胞的调控，然而肠道以及乳腺组织中的菌群生态失调会导致不同疾病的产生，与免疫系统的缺陷及人体屏障的失效共同构成致癌的潜在影响因子[7]。越来越多的研究证明乳腺癌的发生发展与肠道菌群有关，肠道菌群可通过调节各种代谢产物及机体反应加速癌症的进展甚至浸润转移，同时肠道及乳腺的菌群也是联系癌细胞与局部组织之间相互作用的枢纽[8]，此外，有研究报道肠道微生物组成的变化能够促进肠外肿瘤的发展并增强其侵袭性[9]，其中便包括乳腺癌。

2.1. 肠道菌群的组成与乳腺癌

乳腺组织中存在着特定的菌群，Urbaniak 的研究团队使用 16S rRNA 测序及细胞培养的方法分析得出乳腺组织中最丰富的门是变形菌门，其次是厚壁菌门、放线菌门和拟杆菌门，依次递减[10]；Hieken 等人在此基础上报告了浸润性癌旁正常乳腺组织的微生物群与良性病变旁正常乳腺组织的微生物群存在显著差异[11]。同时，Luan 等人在最新的荟萃分析中提到乳腺癌患者与健康患者的肠道菌群丰度有差异，其中普雷沃氏菌科和拟杆菌科的差异显著，拟杆菌属、普雷沃氏菌科、瘤胃球菌属、罗氏菌属、普拉梭菌等构成肠道基石的菌属相对丰度在乳腺癌患者中下降，而丹毒丝菌属的丰度升高[12]；有研究指出肠道

细菌的差异性与年龄及绝经状态有关，对比健康女性，绝经前后乳腺癌患者的肠道菌群组成及丰富度均有差异，绝经前产短链脂肪酸(SCFA)细菌的丰度显著降低[13]，绝经后以乳杆菌属及真/优杆菌属的减少为主[14]。有既往的文章总结了肠道细菌易位的证据，肠道微生物可能会从胃肠道转移到乳房，参与乳腺癌的发生发展[11]。

2.2. 肠道菌群参与乳腺癌的发生发展

2.2.1. DNA 损伤

DNA 损伤可直接或间接地导致细胞的癌变，其中细菌毒素所致的双链断裂以及在氧化应激反应中产生的活性氧(ROS)都能对 DNA 产生不可逆的损伤。Urbaniak 发现从乳腺癌患者组织中培养的表皮葡萄球菌及大肠杆菌分离株能够产生“大肠杆菌素”[15]，由一种革兰氏阴性菌产生的具有 DNA 酶活性的毒素“细胞致死膨胀毒素”(CDT) [16]，这两种细菌毒素具有让肠道上皮细胞的 DNA 双链断裂的能力，细胞周期进入短暂的停滞后形成突变，加剧肿瘤的形成；脆弱拟杆菌和幽门螺杆菌等细菌产生毒素，其产生的活性氧(ROS)则直接损伤消耗 DNA，促使其发生突变[17]。

2.2.2. 类固醇激素

乳腺癌的生长和发展在很大程度上受类固醇激素的调节，雌激素占主要影响因素，约 70%的绝经后乳腺癌患者对雌激素敏感[18]。多项研究证实乳腺癌与肥胖、较高的雌激素水平有关[19]，雌激素通过肝脏代谢，在肝脏中与胆汁结合并排泄到肠道，此结合物在肠道中被具有一组特殊功能的细菌分解，这组细菌具有 β-葡萄糖醛酸酶活性，大多由革兰氏阳性菌如双歧杆菌，少部分革兰氏阴性菌如拟杆菌属组成[20]，分解物质继续通过肝肠循环以游离雌激素的形式被机体重新吸收，到达不同的器官包括乳房[21]，导致女性体内雌激素循环增加，内源性性激素水平提高。此外，这种具有 β-葡萄糖醛酸糖苷酶活性的细菌可参与外源性物质和异种雌激素的解偶联，导致其通过肝肠途径再摄取，从而延长其在体内的停留时间；Key 等人通过对 9 项前瞻性试验的分析发现，绝经后女性循环雌激素浓度的增加和雌激素暴露时间的延长与乳腺癌的高风险有关[22]。肠道菌群能够从膳食多酚中合成雌激素模拟物，这可以激活 ERα 和 ERβ 信号传导，加剧肿瘤的发生[23]，同时也可以参与调节及代谢组织微环境中其他的类固醇激素如雄激素、孕酮和睾酮，通过提高其生物利用度促进对乳腺肿瘤的调控[24]。

2.2.3. 代谢产物

次级胆汁酸由肠道细菌合成，主要包括厚壁菌门和拟杆菌门。具有抑制乳腺癌细胞增殖和侵袭性作用的石胆酸(LCA)由于肠道菌群多样性降低，因此在早期乳腺癌患者体内的水平较低，这种抑制作用通过激活 TGR5 受体实现，同时 LCA 促进氧化磷酸化及三羧酸循环从而抑制上皮－间充质转化(EMT)和血管内皮生长因子(VEGF)的生成[25]，EMT 能够赋予癌细胞迁移和转移潜力以及细胞可塑性和干细胞样特征[26]，VEGF 则通过促进肿瘤细胞的增殖及血管生成加速肿瘤发展，从而促进癌症进展[27]。而通过下调促凋亡蛋白来促进乳腺肿瘤细胞存活的脱氧胆酸在绝经后乳腺癌患者体内浓度较高[28] [29]。另外，多项研究表明各种氨基酸代谢产物及短链脂肪酸(SCFA)能够对乳腺癌产生抑制作用。乳酸杆菌为主的肠道菌群代谢色氨酸产生各种吲哚衍生物，吲哚作为芳烃受体(AhR)受体的配体参与机体免疫调节并通过上调 AhR 受体诱导乳腺癌细胞凋亡抵抗[30] [31]；包括福氏志贺氏菌、索内志贺氏菌、大肠杆菌和链球菌在内的多种菌群通过代谢赖氨酸及精氨酸产生的尸胺在体外和体内均可抑制乳腺癌细胞的增殖、迁移、侵袭和干细胞形成，通过 TAAR 受体诱导间充质细胞向上皮细胞转变干预肿瘤的生长，并减少肿瘤向周围组织的浸润，降低肿瘤远处转移的风险[32]。SCFA 中最有代表性的为乙酸盐、丙酸盐和丁酸盐，多由拟杆菌门产生[33]，作为维持肠道内稳态的重要物质，有助于调节组蛋白脱乙酰酶(HDAC)，从而影响细胞附

着、免疫细胞迁移、细胞因子产生、趋化性和程序性细胞死亡[34]，能够抑制癌细胞增殖并诱导凋亡细胞死亡[35]甚至抑制肿瘤细胞的远处转移[36]，丁酸盐受体 GPR109A 激活会抑制人类乳腺癌细胞中参与细胞存活和抗凋亡信号传导的基因，其缺失会增加乳腺癌的发病率和肺转移，因而 GPR109A 在健康乳腺上皮细胞中表达，但在患有乳腺癌的个体中缺失[37]，丁酸盐参与肠道免疫调节，Tregs 是一种表达转录因子 Foxp3 的 T 细胞，对限制肠道炎症至关重要，丁酸盐则负责维持 Tregs 在肠道的稳态间接调节免疫功能，避免肿瘤的发生[38]。SCFA 如乙酸、丁酸盐充当 G 蛋白偶联受体 FFAR2 和 FFAR3 的同源配体，介导了多种信号通路传导如 Hippo-Yap 及 MAPK 通路调节增殖途径、细胞骨架组织和粘附蛋白的表达从而降低乳腺癌细胞的侵袭潜力，同时其具有将细胞从侵袭性间充质表型转向静止上皮表型的净效应，潜在地限制了转移[39]。

2.2.4. 免疫及炎症反应

肠道微生物诱导的炎症反应被认为是致癌的主要原因，肠道菌群诱导宿主组织产生慢性炎症，刺激细胞增殖，最终可能失调，当与细胞凋亡失败一同出现时，致癌过程便会启动；其甚至能够在远端器官中产生促炎作用[40]，例如肠道微生物从肠道向乳腺组织逆行易位，诱发全身性炎症，促进乳腺肿瘤发生[41]。经 POUTAHIDIS 团队的两次实验证实[42] [43]，小鼠口服人乳中分离培养的罗伊氏乳杆菌可以通过诱导 Foxp3 (+)调节性 T 细胞(Treg)和白细胞介素(Il)-10 的主动免疫耐受限制肠道炎症反应，下调炎症因子水平。随后有实验表明[44]，肠道益生菌能够触发 CD4+CD25+淋巴细胞的抗癌保护，甚至可以通过移植在其他受体中发挥抗癌作用。TNF-α 在乳腺癌中是一个关键的促炎细胞因子，其已被证明可以促进乳腺癌细胞的增殖，抑制宿主对肿瘤的免疫反应，乳腺癌组织中 TNF-α 水平升高也与肿瘤分级高、转移风险增加、治疗效果差和疾病恢复机会低相关[45] [46]。Rao 等人用肠道细菌病原体肝幽门螺杆菌感染 Rag2 缺陷的小鼠成功诱导出乳腺癌的发生，这是因为肠道感染肝幽门螺杆菌诱导 TNF-α 依赖的先天免疫反应，有利于乳腺肿瘤的发生，同时病原菌的感染延长了免疫激活，从而导致环氧化酶 2 (COX-2)和前列腺素 2 (PGE2)的持续升高，增加了易感个体的癌症风险[47]。

中性粒细胞及淋巴细胞在炎症反应中扮演着重要的角色，Rutkowski [48]等人发现在乳腺癌患者身上，共生菌、IL-6、中性粒细胞之间存在相互影响。较高的中性粒细胞与较低的淋巴细胞比例与较低的乳腺癌复发率和死亡率相关[49]。宿主免疫系统通过诱导具有肿瘤潜能的异常宿主细胞死亡，在预防癌变中起关键作用[40]。同时，肠源病原菌感染可以增强 T 细胞的免疫效果以降低宿主的患癌风险[50]。总的来说，肠道菌群诱导全身免疫调节和炎症，参与乳腺癌的发生和进展。

3. 肠道菌群与新辅助治疗

正如前文所述，肠道微生物群可以通过合成不同抗肿瘤化合物通过调节免疫反应和宿主炎症途径来影响癌症发病机制的进展[51]，不少将肠道微生物应用于治疗的研究应运而生，已经有 40 种化疗药物被证实是由肠道菌群代谢的[52]，肠道菌群能够调节化疗、靶向治疗药物的活性、毒性和疗效，如环磷酰胺、顺铂、吉西他滨、伊立替康、5-氟尿嘧啶及曲妥珠单抗、酪氨酸激酶抑制剂，并且可能影响免疫治疗的疗法及毒性，同时改善人体细胞耐药的情况。[53]本综述只讨论新辅助治疗，故只针对部分 CSCO 指南中提到的新辅助治疗药物与肠道菌群之间的相互作用进行详细阐述。

3.1. 环磷酰胺

肠道菌群能够对环磷酰胺的抗肿瘤作用产生正面增益，环磷酰胺通过刺激抗癌免疫反应起作用，该药物通过破坏肠粘膜使革兰氏阳性菌易位，在脾细胞中刺激产生白细胞介素-17 (IL-17)，干扰素 γ (IFN)从

而增强免疫反应[54]，Daillère 等人在小鼠模型中发现使用抗生素降低革兰氏阳性菌丰度会降低机体免疫反应从而降低环磷酰胺的抗肿瘤作用，通过口服革兰氏阳性菌可重建该种抗癌能力[55]。

3.2. 顺铂

顺铂是乳腺癌化疗中常见的药物，抗癌作用相对较强，在抗肿瘤细胞的过程中对自身正常细胞的毒副作用较大，它对革兰氏阴性和革兰氏阳性细菌具有抗菌作用，并可引起肠道菌群失调。[56]有研究表明肠道菌群会影响顺铂的毒性，Zhao 的团队[57]发现厚壁菌门和乳酸杆菌的减少，可能是导致顺铂相关副作用如化疗导致的消瘦及心功能障碍的原因，口服补充乳酸杆菌可防止化疗所致的消瘦，恢复心脏功能。其次，Pflug 等人[58]发现抗革兰氏阳性抗生素对顺铂抗癌活性的产生具有潜在的负面影响，这是由于肠道黏膜屏障破坏后，革兰氏阳性菌的易位以及随后诱导细胞毒性氧反应性物质和致病性 Th17 细胞侵袭肿瘤，这说明革兰氏阳性菌能够有效提高药物的抗癌活性。

3.3. 曲妥珠单抗

曲妥珠单抗是 HER-2 阳性乳腺癌患者的基础靶向用药，Di Modica [59]及研究团队分析了 24 例连续接受含曲妥珠单抗新辅助治疗的 HER-2 阳性乳腺癌，发现新辅助治疗后达到 PcR 的患者较 non-PcR 的患者肠道菌群多样性明显较高，并发现与淋巴细胞浸润、B 细胞、活化 CD4 + T 细胞等相关的免疫特征与菌群多样性呈显著正相关，证明了肠道微生物直接参与曲妥珠单抗有效性的观点，这与 Li 的团队报道的肠道菌群通过调节 CD4 + T 淋巴细胞从而提高化疗敏感性的观点一致[60]。同时该研究团队在小鼠上构建的临床前模型上提示使用万古霉素或链霉素可完全消除曲妥珠单抗对肿瘤生长的抑制作用，在抗生素联合曲妥珠单抗治疗后，肿瘤内 CD4 + T 淋巴细胞和 NK 细胞的募集显著减少。而且由抗生素导致的肠道菌群组成改变会引起肿瘤免疫微环境的改变[61]，研究团队将经抗生素处理小鼠的粪便物质转移到受体小鼠中，在其体内重现了对曲妥珠单抗的反应和肿瘤免疫浸润情况，揭示了肠道微生物群与免疫介导的曲妥珠单抗活性之间的因果关系。

新辅助治疗自 20 世纪 70 年代被引入以来，作为一种肿瘤及腋窝淋巴结降期和检测肿瘤耐药的治疗方法被广泛应用，对乳腺癌预后预测及指导进一步治疗产生重要影响[62]，上述的曲妥珠单抗、环磷酰胺、顺铂等新辅助治疗一线药物的抗肿瘤活性、毒性等都在一定程度上受到肠道菌群所调节，这也预示着肠道微生物群可能作为预测新辅助治疗反应的潜在生物标志物[60]。

4. 益生菌与乳腺癌

基于以上研究及理论支持，口服益生菌与粪菌移植(FMT)成为了预防和治疗乳腺癌生长和转移以及提高乳腺癌化疗、靶向治疗、免疫治疗疗效的主要潜在途径，但粪菌移植所需的条件非常苛刻并且极易加剧患者肠道菌群紊乱甚至引起肠道感染，因此口服益生菌成为更多临床试验的选择。多项研究均报道了在体外模型中益生菌对于肿瘤细胞可能的作用机制，Soltan 及其团队对皮下移植乳腺腺癌肿瘤的小鼠给予干酪乳杆菌或基础悬浮液，持续给药三周，数据分析显示，与对照组相比，肿瘤生长速度明显降低，生存时间明显延长，该试验同时表明口服干酪乳杆菌可显著增加受试小鼠脾细胞培养中 IL-12 和 IFN-γ 的产生($P < 0.05$)，并增加自然杀伤细胞(NK)细胞毒性($P < 0.05$) [63]。de Moreno 等人使用乳杆菌发酵的牛奶喂养试验组的小鼠，肿瘤对照组未接受特殊喂养。在摄食期结束时，小鼠在乳腺中皮下注射肿瘤细胞，注射后 4 天，试验组小鼠继续周期性地接受发酵乳喂养，结果显示，与肿瘤对照组相比，试验组中所有样本的 IL-10 和 IL-4 均升高，IL-6 减少，IL-6 是一种参与雌激素合成的细胞因子。因此，益生菌调节免疫系统和内分泌系统之间的关系(通过 IL-6 减少)，这在雌激素依赖性肿瘤和诱导细胞凋亡中非常重要[64]。如前文所述 TNF-α 是促进乳腺癌发生转移的重要促炎细胞因子，某些益生菌，如乳酸杆菌、双歧杆菌和

链球菌，可以通过靶向抑制关键细胞促炎信号通路的活性来抑制 TNF-α 的转录和释放。[65]来自 Thu [66]的荟萃分析总结了临床试验中益生菌对于乳腺癌的影响，包括乳酸杆菌和双歧杆菌在内的益生菌能够增加乳腺癌患者肠道菌群多样性，显著改善乳腺癌相关淋巴水肿患者的生活质量，肥胖作为乳腺癌的潜在发病因素可通过益生菌服用改善。Juan 等人[67]报道的一项随机对照试验显示，益生菌能有效降低化疗相关认知障碍(CRCI)的发生率，提高患者生活质量。该试验共纳入 162 名患者，并随机分配接受益生菌组(n = 81 [50%])或安慰剂组(n = 81 [50%])，益生菌组的 CRCI 总发生率(80 例患者中 28 例[35%])显著低于安慰剂组(79 例患者中 64 例[81%])。Zeng 探究了益生菌脆弱拟杆菌 839 (BF839)在减少乳腺癌患者化疗相关骨髓抑制和胃肠道毒性方面具有显著作用[68]。截止目前为止，仍有大量的临床试验正在进行，多种新型益生菌的潜在作用正在被挖掘，但当前大多数试验都是在小规模人群和不同年龄和肿瘤阶段的患者中进行的，缺乏大量临床试验数据支持，并且缺少益生菌与乳腺癌疗效之间关联的研究，未来仍需要从多个角度研究微生物群与乳腺癌之间的关系，扩大研究样本量，并结合营养支持等方面为增强乳腺癌的治疗疗效及改善患者生活质量做更多的努力。

5. 不足与展望

乳腺癌作为女性中最常见的癌症，给全球女性的健康及生活质量造成了显著的影响，除了疾病本身，药物带来的副作用及术后并发症也是不可忽视的一环。近年来，腋窝降级治疗(Axillary De-Escalating Treatment)是提高患者术后生活质量，减轻患者心理压力的有效方式，新辅助治疗则是腋窝降级治疗的基础，更是当前“化疗–手术–化疗”治疗模式不可或缺的一环。乳腺癌是一种由多因素导致的疾病，其中肠道菌群是已被证实的能够调节乳腺癌发生发展的重要途径，但近年来人们发现肠道菌群能够对乳腺癌的治疗产生显著影响，尽管其机制复杂多样甚至还有许多方面值得去探索，但不少研究已经着手于肠道菌群对乳腺癌的诊断、预测作用，并利用外来菌群的干预改善疗效。如何有效地利用肠道菌群合理且高效地提高新辅助治疗的疗效仍是待解决的问题，目前已有的研究多基于体外及动物模型，我们需要更多在乳腺癌患者身上的临床研究来确定益生菌的价值，并了解相关机制在预防和治疗中的作用。同时人体肠道菌群的丰富性决定了我们在确定对肿瘤细胞有活性的菌群种类上还有很长的路要走，益生菌的剂量和个体化治疗方案也需要大量多样本的试验来探索。

基金项目

重庆市永川区自然科学基金计划：不同年龄组女性乳腺癌临床病理与预后比较(项目编号：2023ycjckx20010)。

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