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影响乳腺癌复发的宿主相关因素研究进展

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摘 要

肿瘤复发是乳腺癌相关死亡的主要原因。靶向可改变的风险因素以降低乳腺癌复发率是新的研究热点。本综述介绍了影响乳腺癌复发的宿主相关因素的最新发现，目的是为临床医生提供乳腺癌全程管理的新思路，引导他们进一步关注可能改善乳腺癌预后的全方位临床干预措施。

关键词

乳腺癌，休眠，复发，炎症，肥胖，饮食，体力活动，情绪障碍

Research Progress on Host-Related Factors Affecting Breast Cancer Recurrence

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Abstract

Tumor recurrence is the main cause of breast cancer-related death. Targeting modifiable risk factors to reduce breast cancer recurrence rate has become a new research hotspot. In this review, we illustrate the latest discoveries on host-related factors that may influence the recurrence of breast cancer. The aim of this review is to offer clinicians recent insights into breast cancer whole process management and further guide them to focus on the complete clinical intervention measures that might improve breast cancer prognosis.

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Keywords

Breast Cancer, Dormancy, Recurrence, Inflammation, Obesity, Diet, Physical Activity, Emotional Disorder

1. 前言

根据国际癌症研究机构的数据，2020 年起乳腺癌首次超过肺癌成为全球最常见的恶性肿瘤[1]。大部分乳腺癌患者诊断时为早中期或者局部晚期的潜在可治愈病例，并且随着近年来外科技术、放疗及抗肿瘤药物的发展，乳腺癌幸存者(Breast Cancer Survivors, BCS)的预后大为改善，但最新的数据表明，根治治疗后累积复发率仍高达 16.6% [2]。而转移性复发是 90%以上乳腺癌相关死亡的原因[3]。近年来越来越多的证据表明，全身炎症状态、体重、饮食、体力活动和情绪等可改变的风险因素会影响乳腺癌复发。这些宿主相关因素有望成为降低 BCS 复发率的临床干预靶点，本文将相关研究进展做一简要综述。

2. 炎症

2.1. 炎症与休眠

肿瘤复发的主要原因之一是乳腺癌患者在诊断时即携带微转移，这部分播散性肿瘤细胞能够逃避初级治疗以静止状态长期存在，成为休眠癌细胞(Dormant Cancer Cell, DCC) [4]。DCC 的特点是可逆的有丝分裂停滞，在适当的环境下 DCC 能够“苏醒”，恢复其增殖，最终导致肿瘤复发转移[5]。近年来研究炎症在促进乳腺癌休眠细胞的生长和觉醒方面发挥重要作用。

有研究发现利用 3D 离体肝脏微生理系统，对肝细胞、非实质细胞及乳腺癌细胞进行共培养，观察到乳腺癌细胞在该系统中能够实现自发休眠，并且较之聚苯乙烯支架，采用水凝胶支架进入休眠状态的肿瘤细胞比例显著增加，这可能与水凝胶支架促炎因子分泌水平更低有关[6]。利用上述 3D 立体肝脏微生理系统共培养肝星状细胞和乳腺癌细胞，发现活化的肝星状细胞可以通过分泌炎性细胞因子白介素-8，诱导乳腺癌细胞从休眠状态中苏醒[7]。在乳腺癌肝转移的小鼠模型中，发现在休眠环境中自然杀伤细胞有选择性地增加，自然杀伤细胞通过干扰素-γ 信号通路维持休眠，若自然杀伤细胞明显收缩，则活化的肝星状细胞开始积聚，进而导致肝脏中的 DCC 结束休眠[8]。

除了肝星状细胞，中性粒细胞也是最常见的炎症细胞之一，可以通过向细胞外空间释放中性粒细胞外陷阱来杀死有害微生物。在小鼠乳腺癌模型中，烟雾暴露或经鼻滴注脂多糖诱发的持续实验性肺部炎症导致中性粒细胞外陷阱的形成，进一步诱导小鼠肺脏中的 DCC 转化为侵袭性肺转移，抑制中性粒细胞外陷阱形成或消化中性粒细胞外陷阱的支架可以阻断此过程，提示中性粒细胞外陷阱可能是炎症诱导 DCC 觉醒的关键介质[9]。

有研究在小鼠身上建立了一个能够在受控的实验环境中观察原发肿瘤切除产生的手术创伤是否会引发远处解剖部位播散性肿瘤细胞生长的模型，发现手术后诱导的全身炎性反应促进了远隔部位肿瘤的出现，并且围手术期抗炎治疗可显著减少该模型中的肿瘤生长[10]。亦有研究证实乳腺癌原发肿瘤切除可导致微转移爆发，消除炎性分泌因子或在围手术期抗炎治疗可使微转移消退到非生长状态[11]。

2.2. 抗炎治疗

环氧化酶(Cyclo-Oxygenases, COXs)抑制剂是最常见的抗炎药物，目前已有一些应用 COXs 抑制剂改善乳腺癌预后的临床研究[12]。一项转化研究对 38 名早期乳腺癌患者进行为期 11 天的围手术期 β-肾上腺素能拮抗剂(普萘洛尔)和 COX-2 抑制剂(乙哚乙酸)治疗，发现多种与乳腺癌转移复发相关的信号通路被抑制[13]。另一项研究也发现对肥胖患者术中使用非选择性 COX 抑制剂酮咯酸可降低远处转移的发生率[14]。

2.3. 膳食炎症指数

促炎饮食可引起组织水平的炎症，与乳腺癌不良预后有关，而抗炎饮食可以改善炎症以及 BCS 的整体预后[15]。膳食炎症指数是为了标准化评估饮食的炎症潜能而创立的指标。一项研究分析了 530 名接受根治手术的 BCS 的数据，发现术后复发患者的膳食炎症指数显著高于无复发患者，膳食炎症指数与乳腺癌复发风险呈正相关，膳食炎症指数评分较高患者的无病生存率和总生存率明显降低[16]。另一项 Meta 分析亦报告膳食炎症指数与 BCS 复发率和全因死亡率正相关[17]。国内和欧洲的前瞻性队列研究均发现 BCS 的膳食炎症指数越高，全因死亡率和乳腺癌特异性死亡率越高[18] [19]。

C 反应蛋白是最常用的炎症指标，已有研究发现 C 反应蛋白是可以独立预测乳腺癌长期存活的生物标志物[20]。术后辅助治疗期间血清 C 反应蛋白水平与 HR+/HER2-乳腺癌复发风险呈显著正相关[21]。Wu 等发现膳食酸负荷与 C 反应蛋白和 HbA1c 呈正相关，膳食酸负荷可能导致炎症和高血糖的新型饮食因素，其两者都是 BCS 复发和合并症的重要危险因素[22]，该发现为饮食如何影响全身炎症状态提供了一个可能的连接点。

3. 体重

已有多项临床试验证实肥胖和体重增加与 BCS 复发和死亡风险增加有关。Tulay 等的研究表明脂肪肝是乳腺癌复发的危险因素[23]。一项前瞻性研究纳入 6295 名生存期超过 5 年的 ER 阳性 BCS，发现体重增加 ≥ 10%、BMI = 30~34.99 kg/m^2 和 BMI ≥ 35 kg/m^2 与晚期复发风险增加相关，风险比(hazard ratio, HR)分别为 1.24、1.40 和 1.41 [24]。一项 Meta 分析纳入 21 项研究，进一步发现 BMI 与乳腺癌复发风险呈正线性相关，BMI 每增加 1 kg/m^2，复发风险增加约 2%；并且亚组分析发现 BMI 对亚洲女性影响更大，BMI 每增加 1 kg/m^2，亚洲组 BCS 复发风险增加 3.41% [25]。ELIA 等也发现与正常体重 BCS 相比，超重/肥胖 BCS 无转移生存期更短[26]。欧洲一项研究对 13624 名 BCS 平均随访 8.6 年，发现 BMI 每增加 5 kg/m^2，全因死亡率和乳腺癌特异性死亡率分别增加 10% (95% CI: 5%~15%)和 7% (95% CI: 0~15%)；且无论 BMI 如何，腹部肥胖 BCS 的全因死亡率增加了 23% (95% CI: 11%~37%) [27]。

不幸的是目前研究数据显示 63.7%的 BCS 在确诊后体重增加，平均增加 9.07 kg，60.7%的幸存者 BMI 增加 > 1 kg/m^2，超重/肥胖的比例从诊断时的 48.5%上升到调查时的 67.4% [28]。针对这一现状，有研究检验了在接受新辅助化疗的 BCS 中采取预防原发性体重增加的干预措施的可行性和初步疗效，结果显示 88%的参与者对在化疗期间的干预感到满意，干预组的腰围缩小幅度和自我报告的活力得分明显高于对照组，表明在新辅助化疗期间即对 BCS 开始预防性体重管理是可行的，并对患者产生有益影响[29]。

目前对肥胖影响乳腺癌预后的潜在机制仍然知之甚少。已有研究表明肥胖是引起全身和组织水平慢性炎症的常见原因，肥胖患者的局部白色脂肪组织被免疫细胞浸润，包括巨噬细胞和淋巴细胞。因此肥胖脂肪垫类似于慢性损伤组织，可以成为促炎介质的丰富来源，潜在地促进肿瘤生长[30]。Quail 等的研究发现在用高脂饮食诱导肥胖乳腺癌小鼠时，其肺组织中的中性粒细胞浸润，进而促进乳腺癌向肺转移，并且体重减轻可以逆转这种影响[31]。Patricia 等也发现高脂饮食增加了肺脏和肝脏微环境中棕榈酸的可

得性，这可能有助于肿瘤转移性生长[32]。ECKER 等进一步发现在自发性乳腺癌小鼠模型中，与瘦小鼠对比，肥胖小鼠的复发速度更快[33]。Roy 等构建了一个绝经后乳腺癌小鼠模型，对小鼠进行高脂饮食诱导后观察到，与瘦小鼠相比，肥胖小鼠肿瘤潜伏时间更短；其潜在机制可能与肥胖诱发的促血管生成和炎性环境有关；并且应用舒尼替尼靶向治疗可以延长肿瘤潜伏期、增加无瘤生存率[34]。

4. 饮食

4.1. 地中海饮食

地中海饮食(Mediterranean Diet, MD)被认为是最健康的饮食模式之一。一项名为 DIANA-5 的随机对照临床试验评估了地中海饮食在减少乳腺癌复发方面的有效性，该试验纳入 1542 名 ER 阴性且具有高复发风险的 BCS，建议她们坚持 MD，并用健康饮食指数将依从性分为高中低三组，随访 5 年后发现依从性好的亚组复发风险显著低于依从性差的亚组(HR = 0.59, 95% CI: 0.36~0.92) [35]。一项回顾性研究调查了不列颠哥伦比亚省 BCS 坚持 MD 与长期预后之间的关系，发现 MD 依存性高的 BCS 其 15 年生存率(63.1%)高于依存性低者(53.6%) [36]。另有多项最新研究亦证实 BCS 对 MD 的依从度与死亡率呈明显负相关[37] [38]。

MD 的保护机制尚未完全阐明，可能与 MD 中富含的多种营养成分被证实有抗肿瘤活性有关[39]。此外研究表明 MD 可对肠道菌群产生显著且有益的影响，进而发挥抗癌作用[40]。也有学者认为与 MD 可降低氧化应激、提高胰岛素敏感性以及减少促炎细胞因子的分泌有关[41]。有研究发现接受内分泌治疗的 BCS 在食用鱼油、橄榄提取物和姜黄素提取物的混合物 30 天后，血浆 CRP 水平显著降低[42]，这几种食物成分恰恰是 MD 所富含的。

4.2. 其他饮食模式

Foroutan-ghaznavi 等研究了纯素食、“谨慎”(健康)饮食和“西方”(不健康)饮食等三种饮食模式与 BCS 中促转移基因表达水平之间的关系，发现坚持纯素食和“谨慎”饮食模式与 BCS 促转移基因的下调显著相关，而坚持“西方”饮食模式是促转移基因表达上调的风险因素[43]。有 Meta 分析进一步发现，较之“西方”饮食，对“谨慎”饮食更高依从性的 BCS 全因死亡率降低了 22% (HR = 0.78, 95% CI: 0.73~0.84) [44]。

上海一项研究数据显示，对中国膳食宝塔饮食指南和终止高血压膳食疗法依从性更高的 BCS，其总体死亡率和乳腺癌特异性复发/死亡风险降低[45]。亦有研究发现热量限制似乎可以提高 BCS 抗肿瘤免疫力，采用长期斋戒饮食有助于减少肿瘤复发，改善长期预后[46]。

5. 体力活动

越来越多的流行病学数据提示体力活动能够防止 BCS 复发[47]。一些前瞻性观察性研究发现，癌症诊断后的体力活动可能会降低乳腺癌死亡率[48]。另有 Meta 分析显示，体力活动可使 BCS 复发风险降低 48%，全因死亡率降低 24% [49]。其保护机制可能与体力活动能够减重、改善胰岛素抵抗、减轻全身炎症反应、减轻氧化应激等益处有关[50]。最新的研究发现体力活动可诱导内脏代谢重编程，通过限制肿瘤的营养供应来防止转移定植，即产生运动诱导的代谢屏障[51]。另外体力活动可以改善 BCS 焦虑水平和减轻内分泌治疗副反应，有助于提高治疗依从性[52]。

虽然 Wang 等研究显示，与不活动相比，即使少量的体力活动也能降低死亡率[53]。有 Meta 分析进一步发现，较之低强度体力活动(<300 min/周)，中强度(300~500 min/周)和高强度(>500 min/周)的体力活动可以更大程度地降低乳腺癌特异性死亡率和全因死亡率的风险，然而随着体力活动量的增加，收益的

增加趋于平稳[54]。尤其值得关注的是，从诊断前到诊断后减少体力活动可使全因死亡率增加 236% (HR = 2.36, 95% CI: 1.09~5.12) [54]。体力活动和其条件血清已被证明可通过肾上腺素依赖性机制，使乳腺癌细胞中的 Hippo/YAP 信号传导失活，这表明与儿茶酚胺水平升高相关的体力活动可以降低癌细胞在远处组织中形成肿瘤的能力[55]。已有大量研究表明，体力活动能够诱导免疫细胞的抗肿瘤作用，免疫系统对体力活动有很高的反应，在进行体力活动的过程中，大量具有抗肿瘤功能的细胞毒性免疫细胞被动员到循环中杀死循环肿瘤细胞[56]，随着对体力活动对肿瘤转移机制影响的研究不断深入，新的治疗策略将被确定和验证，可能有助于降低 BCS 的复发、转移率，以提高癌症患者的生存率。

6. 情绪

情绪障碍亦会对乳腺癌预后产生不良影响。有 Meta 分析纳入 17 项研究共 282,203 名 BCS，发现抑郁症与 BCS 复发率(HR = 1.24, 95% CI: 1.07~1.43)、全因死亡率(HR = 1.30, 95% CI: 1.23~1.36)和乳腺癌特异性死亡率(HR = 1.29, 95% CI: 1.11~1.49)呈显著正相关；焦虑症与 BCS 复发率(HR = 1.17, 95% CI: 1.02~1.34)和全因死亡率(HR = 1.13, 95% CI: 1.07~1.19)呈正相关，但与乳腺癌特异性死亡率无关；抑郁和焦虑合并症患者全因死亡率(HR = 1.34, 95% CI: 1.24~1.45)和乳腺癌特异性死亡率(HR = 1.45, 95% CI: 1.11~1.90)更高；并且亚组分析表明，临床诊断抑郁症和焦虑症时年龄较小(<60 岁)的患者预后更差；综上，抑郁症和焦虑症是预测乳腺癌复发和存活的独立影响因素[57]。

近年来越来越多的学者认为 BCS 对癌症复发的恐惧是一种独立的情绪障碍，并且与抑郁和焦虑等症状是高度互动的；引导患者应用可增强个人控制感的干预措施有助于预防或减少对癌症复发的恐惧[58] [59]。通过心理治疗等手段减轻 BCS 对癌症复发的恐惧水平成为新的干预靶点[60]。

7. 结语

综合本文研究结果，健康生活方式可以减少 BCS 复发的风险因素，并改善总体健康，这可能转化为预后优势。而且对于 BCS 来说，“术后”阶段是一个漫长而艰难的时期，纳入生活方式干预有助于建立一个生理–心理支持网络。但是目前临床实践中医生很少与患者探讨非药物干预手段，主要原因是缺乏指南指导和重视程度不够。乳腺癌的管理尚未充分发挥其潜力，希望将来风险因素控制逐渐纳入到乳腺癌全程管理体系当中。目前通过风险因素干预减少乳腺癌复发率已进行临床试验，情况见表 1。

Table 1. List of ongoing clinical trials of reducing breast cancer recurrence rate through risk factor intervention
表 1. 通过风险因素干预减少乳腺癌复发率的在研临床试验列表

干预措施	受试人群	试验阶段	试验编号
阿司匹林	HER2 阴性 II-III 期 BCS	III 期	NCT02927249
减重	超重/肥胖 BCS	III 期	NCT02750826
二甲双胍	早期 BCS	III 期	NCT01101438
减重 + MD + 体力活动	非转移性 BCS	III 期	NCT02035631
体力活动	0-III期高复发风险 BCS	未描述	NCT04818359
MD + 体力活动 + 维生素 D	意大利地区 BCS	未描述	NCT02786875

来源：ClinicalTrials.gov。

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