

DOI: 10.16781/j.CN31-2187/R.20240328

• 专题报道 •

结直肠癌非遗传危险因素研究进展

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[摘要] 结直肠癌是全球范围内最常见的恶性肿瘤之一, 近年来其发病逐渐呈现年轻化趋势。非遗传因素在结直肠癌发生中起着重要作用, 例如饮食习惯、生活方式和肠道菌群等。饮食因素与结直肠癌发生具有密切关系, 一般认为纤维摄入不足、红肉和加工肉类摄入过多等是导致结直肠癌发生的主要高危因素, 蔬菜、水果是有益因素, 而钙剂、维生素 D、乳制品和不同饮食模式对结直肠癌发生的作用尚有争议。此外, 肥胖、吸烟、饮酒、缺乏体育锻炼等问题与结直肠癌风险有一定关联。肠道菌群的失调也被认为与结直肠癌的发生有关。优化饮食习惯、维持健康的生活方式有助于降低结直肠癌的发生风险。非甾体抗炎药、雌激素补充可能对降低结直肠癌风险有益, 对某些高风险个体采用药物干预可能是一种有效的预防措施。

[关键词] 结直肠肿瘤; 环境因素; 饮食因素; 肠道菌群

[引用本文] 卫佳慧, 赵优冬, 张桓伟, 等. 结直肠癌非遗传危险因素研究进展[J]. 海军军医大学学报, 2025, 46(1): 32-39. DOI: 10.16781/j.CN31-2187/R.20240328.

Non-genetic risk factors of colorectal cancer: research progress

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[Abstract] Colorectal cancer (CRC) is one of the most common malignant tumors worldwide, and its incidence has been increasing in recent years, especially among young adults. Non-genetic factors, such as dietary habits, lifestyle and intestinal flora, play an important role in the development of CRC. Dietary factors have a close relationship with CRC development. Insufficient fiber intake and excessive consumption of red and processed meat are generally considered major high-risk factors for CRC, while vegetables and fruits are considered as beneficial factors. The roles of calcium supplements, vitamin D, dairy products, and different dietary patterns in the development of CRC are still controversial. Furthermore, obesity, smoking, alcohol consumption, and lack of physical exercise are also associated with the risk of CRC. The imbalance of intestinal flora is also believed to be associated with the development of CRC. Optimizing dietary habits and maintaining a healthy lifestyle can significantly reduce the risk of CRC. Non-steroidal anti-inflammatory drugs and estrogen supplementation may have beneficial effects in reducing the risk of CRC. For certain individuals at high risk, pharmacological intervention may serve as an effective preventive measure.

[Key words] colorectal neoplasms; environmental factors; dietary factors; intestinal flora

[Citation] WEI J, ZHAO Y, ZHANG H, et al. Non-genetic risk factors of colorectal cancer: research progress[J]. Acad J Naval Med Univ, 2025, 46(1): 32-39. DOI: 10.16781/j.CN31-2187/R.20240328.

结直肠癌(colorectal cancer, CRC)是全球第三大常见恶性肿瘤, 也是第二大癌症相关死亡的原因^[1]。根据 GLOBOCAN 2020 的数据, 全球在

2020 年新发 CRC 病例 193 万例, 死亡病例 93.5 万例^[1]。同年, 我国 CRC 新发病例数和死亡病例数在恶性肿瘤中分别居于第 2 位和第 5 位^[1]。此外,

[收稿日期] 2024-05-15 **[接受日期]** 2024-11-21

[基金项目] 国家自然科学基金(82170567, 82300627), 国家博士后创新人才支持计划(BX20230482), 上海市自然科学基金面上项目(23ZR1478700)。Supported by National Natural Science Foundation of China(82170567, 82300627), National Postdoctoral Program for Innovative Talents(BX20230482), and General Program of Natural Science Foundation of Shanghai(23ZR1478700)。

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越来越多的研究表明,CRC发病率呈现出年轻化趋势。虽然大多数新诊断的CRC(56.6%)发生在50~70岁的成年人中,但自1990年以来,世界上几乎所有地区的早发性结直肠癌(early onset colorectal cancer, EoCRC)(50岁以下发病)的发病率和死亡率都有所增加,东亚15~49岁人群的发病率从3.9/10万增加到10.1/10万^[2]。预计到2030年,在全球范围内,早发性肠癌将占结肠癌的11%和直肠癌的23%^[3]。

CRC的发生是一个多因素、多阶段的过程,是遗传因素与非遗传因素相互作用的结果。饮食习惯、生活方式、肠道菌群等非遗传因素对CRC的发生起着重要作用。研究表明,约有60%~65%的散发性CRC是由可改变的非遗传因素引起的^[4]。本文对CRC发生、发展的相关非遗传影响因素进行系统归纳和总结,以期对CRC的一级预防提供指导。

1 饮食因素

大量流行病学研究表明,全球大部分CRC病例与已知的饮食因素有关。世界癌症研究基金会(World Cancer Research Fund, WCRF)和美国癌症研究所(American Institute for Cancer Research, AICR)联合发布的《饮食、营养、身体活动与癌症预防全球报告》(2018版)指出,部分食物和营养素的摄入与结直肠肿瘤的风险有关^[5]。钙、纤维、牛奶和全谷物摄入可以降低患CRC的风险,而红肉和加工肉类摄入则会增加患CRC的风险,有证据表明摄入维生素、水果和蔬菜具有潜在的化学预防作用^[5]。营养和食物也可能相互作用,作为一种饮食模式影响CRC的发病。

1.1 食物和营养素

1.1.1 膳食纤维 Veettil等^[6]通过对45项研究进行分析发现,随着总膳食纤维摄入量的增加,CRC发病风险逐渐降低。膳食纤维可来源于谷类、蔬果及豆类食物,各种膳食纤维对CRC发病具有不同作用。在NIH-AARP饮食与健康队列研究中,摄入全谷物与CRC风险呈负相关,而不是其他来源的膳食纤维^[7]。2018年WCRF/AICR报告通过meta分析发现,全谷物摄入量每增加90 g/d,CRC风险降低17%^[5]。国内关于膳食纤维与肠癌的研究结果显示,中国成年人摄入大量膳食纤维,尤其是来自蔬菜和水果的膳食纤维,能够降低CRC患病风

险^[8]。此外,有研究表明膳食纤维的抗癌作用可能与其对肠道菌群的影响有关,肠道菌群发酵产生的短链脂肪酸,如丁酸、乙酸和丙酸等,能够调节免疫系统和代谢,从而降低CRC的风险^[9]。同时,膳食纤维发酵产生的丁酸盐在结肠细胞中具有能量供应和表观遗传功能,可以作为组蛋白脱乙酰酶抑制剂影响细胞凋亡和增殖,发挥抗癌作用^[9]。

1.1.2 钙剂和乳制品 钙对CRC的长期作用机制可能是它能够结合游离胆汁酸、游离脂肪酸和血红素铁,减少它们对结直肠的毒性作用^[10-11]。高钙摄入量与CRC风险降低显著相关。Lopez-Caleya等^[12]对37项病例对照研究进行分析,结果表明每天摄入300 mg钙可使CRC风险降低6%($OR=0.94$, 95% CI 0.92~0.97),每天摄入100 IU维生素D可使CRC风险降低4%($OR=0.96$, 95% CI 0.93~0.98)。一项针对韩国人的大规模前瞻性队列研究发现,摄入超过每日推荐摄入量的钙的女性患CRC的风险降低^[13]。但Lappe等^[14]研究表明,补充维生素D3和钙并没有显著降低患CRC的风险。

2018年WCRF/AICR报告对10项研究进行的剂量-反应关系meta分析表明,乳制品每日摄入量每增加400 g,CRC发病风险降低13%($RR=0.87$, 95% CI 0.83~0.90)^[5]。最近一项前瞻性队列研究对11万余人随访9.4年发现,乳制品蛋白质摄入量与CRC风险呈负相关($HR_{Q4:Q1}=0.80$, 95% CI 0.67~0.94),其机制可能与乳制品中蛋白质和钙的摄入以及对胰岛素样生长因子1途径的影响有关^[15]。截至目前,关于乳制品摄入能否降低CRC风险的证据在全球范围内并不一致。一项来自我国人群的前瞻性队列研究并未发现增加乳制品摄入量与CRC发病风险降低有显著性关联^[16]。

1.1.3 红肉和加工肉类 大量研究表明摄入红肉和加工肉类与CRC患病率增加有关。2018年WCRF/AICR报告通过meta分析发现,红肉和加工肉摄入量每增加100 g/d,患CRC的风险就会增加12%^[5]。欧洲有关癌症与营养的前瞻性调查结果提供了强有力的证据:与不吃肉或偶尔吃肉的人相比,经常吃肉的人患CRC的风险高出20%^[17]。Farvid等^[18]纳入148项前瞻性研究进行了系统综述和meta分析,结果发现红肉和加工肉的总摄入量与结肠癌($RR=1.21$, 95% CI 1.09~1.34)、直肠癌($RR=1.26$, 95% CI 1.09~1.45)的发生风险显著相关。

相比之下,摄入家禽和鱼类可能对降低CRC发病率有一定作用^[17]。有研究发现,红肉中的某些化合物可能会在体内产生烷基化损伤,并诱导Kirsten大鼠肉瘤病毒癌基因同源物(Kirsten rat sarcoma viral oncogene homolog, *KRAS*)、磷脂酰肌醇-3激酶催化亚基 α 基因(phosphoinositide-3-kinase, catalytic, α ; *PIK3CA*)发生致癌突变,从而促进肿瘤的发展^[19]。

1.1.4 其他 除了增加膳食纤维摄入量、减少红肉和加工肉类摄入外,食用水果和蔬菜可能会降低CRC的发病率,这可能与水果和蔬菜含有特定微量营养素有关,如维生素、纤维素和多酚等^[20]。维生素C是一种有效的抗氧化剂,可以降低活性氧的水平,抑制脂质过氧化和减少硝酸盐。纳入6项研究的剂量-反应meta分析显示,每天摄入40 mg维生素C可降低6%的CRC风险($RR=0.94$, 95% CI 0.89~0.99)^[5]。

1.2 饮食模式

1.2.1 高脂饮食 高脂饮食与CRC之间的相关性存在争议。一项大规模前瞻性队列研究评估了高脂饮食和CRC风险之间的关系,结果表明高饱和脂肪酸摄入会增加CRC风险($HR=1.22$, 95% CI 1.02~1.46)^[21]。然而,也有报道膳食脂肪和脂肪酸对CRC的风险没有明显影响^[22]。Lu等^[23]研究发现,膳食中二十碳五烯酸、二十二碳六烯酸和二十二碳五烯酸高摄入量与CRC低风险相关,而n-6/n-3多不饱和脂肪酸比值和反式脂肪酸与CRC高风险相关。有研究报道,高脂饮食通过诱导小鼠肠道微生物生态失调、代谢组失调(溶血磷脂酸升高)和肠道屏障功能障碍来驱动结直肠肿瘤的发生^[24]。

1.2.2 高糖饮食 Yuan等^[25]对来自美国2项前瞻性队列研究的数据进行分析,发现含糖饮料饮用量和总果糖摄入量与近端结肠癌症的发病率和死亡率呈正相关,但在远端结肠或直肠中没有观察到这种现象。日本一项大规模队列研究也没有观察到增加糖摄入量与CRC风险之间有任何明确的关联,但对不同性别、不同部位肿瘤的分析显示女性直肠癌风险与总糖摄入量呈正相关($HR_{QS:QI}=1.75$, 95% CI 1.07~2.87),因此不能排除总糖摄入量较高的女性直肠癌风险增加的可能性^[26]。这些研究结果的差异可能源于多种因素,包括研究人群的种族

和地理差异、评估糖摄入量的方法等,因此还需要更多研究来进一步探索糖摄入对CRC风险的影响。

1.2.3 地中海饮食(Mediterranean diet, MD) MD是一种起源于地中海沿岸的健康饮食模式,这种饮食方式着重于植物性食物的高比例摄入,包括水果、蔬菜、全谷物、豆类和坚果等,并且以橄榄油作为主要的脂肪来源,越来越多的研究表明长期坚持MD可以有效预防癌症。一篇纳入13项前瞻性队列研究的meta分析表明,坚持MD与降低CRC发病率有关^[27]。与MD依从性最低组相比,MD依从性最高组出现CRC的 RR 为0.90(95% CI 0.84~0.96),出现直肠癌的 RR 为0.82(95% CI 0.71~0.95),提示MD对直肠癌的保护作用确切^[27]。然而,一项纳入120 852名荷兰受试者的前瞻性队列研究对受试者进行20年随访发现,MD依从性升高与CRC风险降低并无显著关联^[28]。有研究报道,橄榄油是MD的核心,橄榄油的酚类和脂类部分都含有多种抗氧化和抗癌物质,可以防止CRC的发展^[29]。

2 不良生活方式

2.1 饮酒 研究表明酒精饮料中的乙醇是CRC的危险因素,其代谢物乙醛已被WHO列为致癌物质。Deng等^[30]通过孟德尔随机化分析评估了东亚人群中饮酒与CRC风险的潜在因果关系,发现与不饮酒者相比,饮酒者CRC风险增高($OR=1.39$, 95% CI 1.21~1.60)。此外,对北美、欧洲和亚洲的14项队列研究进行的meta分析表明,即使是少量饮酒(乙醇摄入量 ≤ 10 g/d)也与发生CRC的风险小幅增加有关($RR=1.04$, 95% CI 1.01~1.06)^[31]。研究表明,在日本乙醇摄入量 ≥ 45 g/d与CRC风险相关的 RR 为2.09(95% CI 1.65~2.64)^[32],而在北美和欧洲为1.41(95% CI 1.16~1.72)^[33]。这可能与亚洲人群存在较多乙醛脱氢酶2(aldehyde dehydrogenase 2, ALDH2)变异体ALDH2*2有关,这种变异体导致乙醇代谢过程中乙醛积累,增加了患癌风险。然而,ALDH2*2变异体携带者饮酒后可能会出现面部发红、恶心或头痛等不适,从而阻止了他们频繁饮酒。尽管这种变异体增加了乙醛积累和癌症风险,但它同时也可能因为减少了乙醇摄入,而实际上降低了CRC的风险。一项meta分析显示,ALDH2*2变异体携带

者患CRC的风险降低约20%^[34]。

2.2 吸烟 吸烟与CRC的发病率和死亡率增加有关。烟草致癌物质(如多环芳香烃)可形成DNA加合物,对DNA造成不可逆损伤。Vajdic等^[35]对106项观察性研究进行meta分析发现,与从不吸烟者相比,吸烟者患CRC的风险增加($HR=1.18$, 95% CI 1.11~1.25),并且吸烟者死于CRC的风险增加。另一项meta分析发现,与不吸烟者相比,当前吸烟和既往吸烟者CRC患病风险的 RR 分别为1.14和1.17,CRC风险随吸烟强度和持续时间呈线性增加;与当前吸烟者相比,戒烟超过25年者罹患CRC的风险显著降低^[36]。同时,吸烟对CRC风险的影响可能因肿瘤的部位不同而有所区别。一项基于10个欧洲国家的队列研究发现,当前吸烟与近端结肠癌($HR=1.19$, 95% CI 1.05~1.34)和直肠癌($HR=1.27$, 95% CI 1.14~1.42)的风险升高有关,但与远端结肠癌风险无关($HR=1.08$, 95% CI 0.94~1.23)^[37]。

2.3 缺乏体育锻炼 近年来,有研究发现久坐不动、缺乏体育锻炼已经成为CRC的危险因素之一。体育活动通过降低性激素水平、降低胰岛素敏感性和增加结肠蠕动来降低患癌症的风险。Moore等^[38]对来自欧美的12项队列研究数据进行分析,共纳入144万人,发现与休闲时间体力活动水平处于后10%的人群相比,处于前10%的人群结肠癌发病风险降低了16%($HR=0.84$, 95% CI 0.77~0.91),直肠癌发病风险降低了13%($HR=0.87$, 95% CI 0.80~0.95)。Hidayat等^[39]开展的一项meta分析发现,从儿童时期开始,终身体育锻炼可以降低罹患结肠癌的风险($RR=0.75$, 95% CI 0.69~0.82)。此外,有研究表明增加体育锻炼还可降低CRC患者的死亡风险^[40]。

2.4 肥胖 我国居民营养与慢性病健康状况报告指出,居民超重、肥胖问题不断凸显,城乡各年龄组居民超重、肥胖率持续上升^[41]。BMI和腰围是最常用的2个评估肥胖的指标。2018年WCRF/AICR报告纳入了38项研究,分析了BMI与CRC发病风险的剂量-反应关系,发现BMI每增加 5 kg/m^2 ,患CRC的风险增加5%($RR=1.05$, 95% CI 1.03~1.07)^[5]。

3 肠道菌群

据估计,人类肠道中的微生物种类超过2 000

种^[42]。已有研究表明,CRC患者肠道组织中大肠埃希菌、产肠毒素脆弱拟杆菌(*enterotoxigenic Bacteroides fragilis*, ETBF)、具核梭杆菌、厌氧消化链球菌、解链食子酸链球菌、粪肠球菌等肠道微生物与CRC发生和发展有关^[43-44]。肠道微生物丰度的改变可促进慢性炎症和致癌代谢物的产生,从而导致肿瘤的发生。

Arthur等^[45]发现含聚酮合酶(*polyketide synthase*, *pks*)基因组岛的大肠埃希菌(*pks*⁺大肠埃希菌)在CRC和炎症性肠病患者的结肠黏膜中富集,并且*pks*⁺大肠埃希菌可以诱导无菌IL-10缺陷小鼠的肿瘤发生。一项meta分析发现,与健康患者相比,CRC患者粪便中含有*pks*的大肠埃希菌显著富集^[46]。*pks*负责大肠埃希菌毒素的合成,这些毒素可以通过引起双链DNA断裂直接攻击宿主DNA,导致突变频率和CRC风险增加^[47]。大肠埃希菌毒素诱导的DNA交联如果修复失败,会导致大规模DNA损伤和染色体不稳定性^[48]。事实上,染色体变异和由此产生的拷贝数变异是大多数散发性CRC的主要特征(超过85%),在早期恶性肿瘤中也观察到类似现象^[49]。

脆弱拟杆菌与大肠埃希菌一样,是人类结肠微生物群中普遍存在的成员,约占结肠细菌的0.1%~0.5%^[49]。ETBF产生脆弱拟杆菌毒素,与CRC有关。研究发现,与健康对照组相比,结直肠癌患者的ETBF阳性率增加^[50-52]。与某些微生物(如具核梭杆菌)不同,CRC患者肿瘤中的ETBF与邻近正常组织相比并未显著富集^[50],ETBF通常在结肠大面积定植^[51]。Cao等^[53]报道了ETBF通过外泌体miRNA-149-3p介导炎症性肠病和CRC发生、发展。有研究报道,梭状芽孢杆菌产生的代谢物脱氧胆酸可抑制CD8⁺T细胞的抗肿瘤免疫反应,从而促进CRC发展;而通过胆汁酸螯合、敲除细菌脱氧胆酸生物合成途径的基因或利用噬菌体靶向清除梭状芽孢杆菌可以消除这种促肿瘤作用^[54]。这为癌症治疗提供了新方向。

具核梭杆菌在CRC患者的粪便和肿瘤组织中均含量丰富。一项meta分析结果显示,CRC患者中具核梭杆菌的丰度比健康人群增加^[46]。有研究者使用体外癌症进展模型发现,具核梭杆菌刺激CRC细胞的生长,而不影响癌前腺瘤细胞^[55]。Wang等^[56]揭示了在CRC的发生、发展过程中,

具核梭杆菌能促进肿瘤细胞的增殖和代谢,重塑免疫微环境,促进肿瘤的转移和耐药。Ternes等^[57]研究发现,具核梭杆菌还可通过其代谢产物甲酸盐增强芳香烃受体信号转导和癌细胞干性,促进CRC进展。

4 其他非遗传因素

大量研究表明,非甾体抗炎药可抑制CRC发生。阿司匹林是其中一种代表性药物,其对结肠和直肠上皮细胞具有抗增殖和促凋亡作用。在过去的十年中,阿司匹林已被用作降低CRC风险的一级预防策略。对于高风险林奇综合征致病基因携带者及所有年龄在50~70岁且具有CRC高危因素的个体,应考虑使用阿司匹林进行预防^[58]。Shah等^[59]开展的一项meta分析表明,高剂量(至少500 mg/d)和中高剂量(至少300 mg/d)阿司匹林均可显著降低CRC发病率,OR分别为0.71(95% CI 0.52~0.96)和0.72(95% CI 0.55~0.94)。然而,使用非甾体抗炎药可能会增加消化道出血等不良事件的发生风险,其最佳剂量和长期服用的安全性仍需更多研究来确定。

雌激素替代治疗和生育史已被证明可降低绝经后女性的CRC风险^[60]。在临床前研究中,围绝经期激素疗法与一些性激素相关癌症有关。Tian等^[61]对38项研究中的28486名绝经后妇女进行分析后发现,使用雌激素与CRC风险降低相关(OR=0.65, 95% CI 0.53~0.79)。Li等^[62]发现,雌激素促进小鼠肠道中的麦芽香肉杆菌的定植,并通过增加维生素D3的产生来发挥其抗CRC的作用。

5 EoCRC

EoCRC是指发病年龄<50岁的CRC,占有CRC病例的10%,其更具侵袭性,诊断时更多处于晚期,且肿瘤的区域转移和远处转移风险相对较高。近20年来,全球EoCRC的发病率升高,但仅约20%的EoCRC与遗传性综合征(如林奇综合征)或CRC、结直肠晚期腺瘤家族史有关^[63]。非遗传危险因素是EoCRC发病的主要因素,主要包括饮食、肠道菌群、久坐、肥胖等。此外,许多其他潜在的危险因素也被认为与EoCRC有关,包括抗生素的大量使用,更普遍的环境毒素,以及增多的剖宫产和其他外科手术等^[64]。

EoCRC的发病可能与疾病相关风险因素的早期暴露有关。研究表明,高脂肪饮食使EoCRC风险增加了近1倍(OR=1.98, 95% CI 1.13~3.49)^[65]。美国护士健康队列研究表明,西方化饮食与直肠早期腺瘤和高风险型早期腺瘤的风险增加相关^[66]。大量证据表明EoCRC发病率升高与影响肠道微生物群的特定饮食因素和饮食模式有关^[44]。抗生素对肠道微生物有重大影响,因此,抗生素的大量使用也对EoCRC风险有一定影响^[64]。越来越多的证据表明肥胖是EoCRC的危险因素^[67]。青少年和成年期的长期久坐行为与EoCRC的风险较高有关^[68]。代谢综合征的患病率在年轻人中有所增加,并与EoCRC相关^[69]。另外,饮酒也是EoCRC的重要危险因素。纳入9项研究的系统综述和meta分析发现,饮酒与EoCRC显著相关(RR=1.71, 95% CI 1.62~1.80)^[70]。值得注意的是,EoCRC与晚发性CRC的风险因素存在重叠,但EoCRC患者在更早的年龄就表现出这些风险因素的影响^[71]。因此,对于年轻群体而言,了解和改善这些风险因素可能对预防EoCRC具有重要意义。

6 小结

CRC近年来发病率呈上升趋势,非遗传因素是影响CRC发生和进展的重要因素,但目前对于其具体的影响机制还需要进一步研究。寻找可改变的非遗传危险因素对CRC的预防具有重要意义,随着研究的深入和科技的发展,更多的危险因素将会被发现。我国需加强CRC相关知识普及,提高公众的健康意识,推广健康饮食和生活方式,并探索其他可能的预防措施,如药物预防等。研究人员可以探索特定肠道微生物对CRC风险的影响,并研发相应的微生物组检测方法和基于肠道微生物群的防治策略,为CRC的早期筛查和预防提供有效手段。

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[本文编辑] 孙 岩