·综述·

结直肠癌的环境及遗传影响因素研究进展

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【摘要】 结直肠癌是全球性的公共卫生问题，对人类健康构成严重威胁。发达国家与地区的结直肠癌发病率常位居前列，且部分发展中国家发病率亦急剧上升。结直肠癌的发生与饮食、生活方式等环境因素以及遗传因素密切相关，基因-环境交互作用也对其发生有一定的调控作用。目前已有较多关于结直肠癌影响因素的研究，本文对已有研究进行综述，从环境因素、遗传因素及基因-环境交互作用出发，探讨上述因素与结直肠癌发病风险的关联，为结直肠癌的预防提供一定证据。流行病学揭示的结直肠癌环境危险因素为肠癌的群体预防提供了更多依据，测序、组学等技术的不断发展则为结直肠癌遗传易感性的解析提供了新的契机，两者的有机结合有利于构建更为精准的风险预测模型，并制定个体化干预方案，以达到降低结直肠癌疾病负担的最终目标。

【关键词】 结直肠肿瘤；环境因素；遗传因素；基因-环境交互作用
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Progress of research on the environmental and genetic influencing factors of colorectal cancer

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【**Abstract**】 Colorectal cancer is a global public health issue which possesses serious challenge. The incidence of colorectal cancer in developed countries and regions stands in the forefront worldwide, and has been rising sharply in some of the developing countries. It is unanimously recognized that the occurrence of colorectal cancer is closely related to environmental factors as diet and lifestyle, genetic factors, and gene-environment interactions of the people. Since there have been many studies on the influencing factors of colorectal cancer, the current review aims at providing evidence on colorectal cancer prevention by evaluating the relationships between the influencing factors and colorectal cancer, based on the published literatures. Environmental risk factors revealed by previous epidemiological studies facilitate the population-based prevention programs against colorectal cancer. The developments of sequencing and omics technologies provide more chances to illustrate the genetic susceptibility of colorectal cancer. With both, we are able to construct more accurate risk prediction models and subsequently developing personalized intervention plans to achieve the ultimate goal of reducing the burden of colorectal cancer.

【**Key words**】 Colorectal neoplasm; Environmental factors; Genetic factors; Gene-environment interactions
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结直肠癌（Colorectal Cancer，CRC）是严重威胁人类健康的恶性肿瘤。据国际癌症研究机构（International Agency for Research on Cancer，IARC）评估，2018年全球有180万结直肠癌新发病例和88万死亡病例，居肿瘤发病顺位第3位，死亡顺位第2位，是全球性的公共卫生问题[1]。结直肠癌的发生与经济水平、生活方式等环境因素息息相关，澳大利亚、新西兰、欧洲地区、北美地区的发病率多年来居全球前列[2]。近年来，由于经济和营养转型、生活方式西化及人口老龄化，部分发展中国家的结直肠癌发病率亦急剧增加[3]。除此之外，遗传因素也在一定程度上决定了结直肠癌的发病风险。结直肠癌遗传度为12%～35%[4]。结直肠癌患者的一级亲属患肠癌的风险比一般人群高2～4倍[5-6]。鉴于结直肠癌的发生与环境及遗传因素密不可分，本文将从环境、遗传及基因-环境交互作用出发，阐述结直肠癌影响因素的流行病学研究结果，为结直肠癌的预防提供更多证据。

一、环境因素与结直肠癌发病风险的关联

1. 饮食因素：红肉和加工肉类中的一些元素被认为有致癌作用，包括防腐剂（如硝酸盐、亚硝酸盐）、肉类加工和烹饪过程中产生的化学物质（如杂环胺和多环芳烃）等。IARC将红肉和加工肉类列为致癌物，认为其与癌症特别是结直肠癌发病风险增加相关。基于约400项队列研究的荟萃分析表明，每天摄入100 g红肉与加工肉类会使结直肠癌发病风险增加12%，且加工肉类可能要比红肉更容易导致结直肠癌，这可能是由于制作方法（烟熏、腌制）暴露于致癌物质所致[7]。

2018年，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）的专家报告指出食用富含膳食纤维的食物可以预防结直肠癌[8]。荟萃分析表明，与饮食中含膳食纤维较低者比，摄入较高含量膳食纤维的人群患结直肠肿瘤的风险可降低12%～28%[9-10]。WCRF/AICR进一步量化了这种关联，指出每天每增加90 g全谷物食物摄入可使结直肠癌的风险降低17%[7]。膳食纤维预防结直肠癌的潜在机制包括增加粪便的体积、加快粪便排出，从而减少潜在有毒致癌物与结肠上皮的接触时间。此外，膳食纤维也可与消化过程中的有害副产品如次级胆汁酸等结合，降低其对肠上皮细胞的致癌作用[9]。

钙被认为能够在结肠环境中结合游离脂肪酸和胆汁酸等化合物，限制其致癌潜力，同时也被证实能够抑制DNA损伤及细胞增殖，诱导分化和凋亡，从而降低结直肠癌的风险[11-12]。与摄入较少的乳制品和牛奶相比，较高的乳制品及牛奶的摄入可使结直肠癌的风险降低约20%[13]。这种关联主要归因于乳制品中较高的钙含量[14]。维生素D可以促进钙的吸收。有关饮食中补充维生素D和循环25-羟基维生素D水平的研究表明，循环25-羟基维生素D水平与结直肠癌发病风险之间存在负相关关系，维生素D可降低结直肠癌发病风险[15]。

此外，鱼类的摄入也与结直肠癌发病风险相关。每天摄入100 g鱼类可使结直肠癌发病风险降低11%（95%*CI*：1%～20%）[7]。鱼类尤其是海洋鱼类对结直肠癌的保护作用很可能与海洋ω-3脂肪酸有关。对美国成年人进行的大型前瞻性研究表明，与海洋ω-3脂肪酸摄入量＜0.15 g/d相比，摄入量至少为0.35 g/d者结直肠癌发病风险可降低43%[16-17]。蔬菜和水果的摄入也有较微效的结直肠癌预防作用。AICR基于10项研究的荟萃分析表明，每天摄入100 g不含淀粉的蔬菜与水果可使结直肠癌发病风险降低2%（95%*CI*：1%～3%）[18]。动物实验表明膳食脂肪在增加结肠细胞增殖和致瘤性方面具有一定作用[19-20]，但流行病学研究尚未显示饮食脂肪摄入与结直肠癌发病风险之间存在明确的关联关系[21]。

鉴于多种食物与结直肠癌的风险相关，近年来，学界进一步研究了饮食模式对结直肠癌发病风险的影响。研究表明，以蔬菜水果、鱼类、五谷杂粮、豆类和橄榄油为主的地中海饮食（Mediterranean Diet, MED Diet）模式与结直肠癌发病风险呈负相关[22-23]。坚持地中海饮食模式可使结直肠癌发病风险降低18%（*RR*＝0.82，95%*CI*：0.75～0.88）[24]。来自35 372名英国女性的队列研究对地中海饮食进行评分（范围0～10分），结果表明饮食评分每升高2分，结直肠癌发病风险可降低12%（*HR*＝0.88，95%*CI*：0.78～0.99）[25]。最新的荟萃分析表明，阻止高血压膳食疗法（Dietary Approaches to Stop Hypertension, DASH）也具有降低结直肠癌发病风险的作用，相对于依从性不高的个体，遵循DASH饮食者的结直肠癌发病风险降低20%（*RR*＝0.80，95%*CI*：0.74～0.85）[26]。哈佛大学Nurses' Health Study（NHS）及Health Professionals Follow-up Study（HPFS）的数据显示，替代性健康饮食指数-2010（The Alternative Healthy Eating Index, AHEI-2010）、替代性MED Diet、DASH饮食评分较高者结直肠癌发生风险减少5%～11%（*HR*值分别为0.95、0.89、0.89）[27]。而长期西化饮食模式（饮食中红肉和加工肉类、精制谷物、苏打水、脂肪含量高，水果、蔬菜和全谷物制品含量低）则可使得肠癌风险增加50%～60%[28-29]。另一项研究利用NHS、HPFS两个队列研究的数据构建了经验性饮食炎症模式（empirical dietary inflammatory pattern, EDIP）评分来估计饮食的致炎潜能，结果表明高水平促炎饮食摄入与结直肠癌发病风险升高相关（最高相对于最低五分位EDIP评分，结直肠癌的*HR*＝1.30，95%*CI*：1.12～1.55）[30]。

2. 生活方式因素：重度饮酒已被确立为结直肠癌的危险因素[31]。最新一项饮酒与结直肠癌发病风险的荟萃分析表明，与不/偶尔饮酒（≤1 g/d）相比，重度（每天2～3杯）或重度以上饮酒（每天＞3杯）与结直肠癌发病风险显著增加有关[*OR*值（95%*CI*）分别为1.11（0.99～1.24）、1.25（1.11～1.40）][32]。WCFR/AICR的最新专家报告指出，重度饮酒与结直肠癌发病风险升高相关且呈现剂量依赖关系：每天饮用40、50、60 g酒精，其结直肠癌发病风险分别增加25%、41%、60%[8]。

吸烟与结直肠癌发病风险增加相关，且作用期较长。来自24项前瞻性队列研究的荟萃分析表明，吸烟者患结肠癌、直肠癌的风险将分别增加9%、24%，且具有明显的剂量效应关系[33]。相较于不吸烟者，当前吸烟者的结直肠癌发病风险显著增加38%，过去吸烟者结直肠癌发病风险增加18%[34]，且曾经吸烟的人在戒烟后的25年内仍有较高的结直肠癌发病风险[35]。在被动吸烟者中，也观察到了类似的关联，被动吸烟者患结直肠癌的风险增加14%，且男性被动吸烟者患结直肠癌的风险高于女性[36]。

超重/肥胖同样被认为是结直肠癌的危险因素[37]。最近的荟萃分析表明，体重每增加5 kg，结直肠癌发病风险将增加2%，BMI每增加5.0 kg/m^2，结直肠癌发病风险将增加6%，成年期较高的全身和腹部脂肪是结直肠癌的危险因素，这些关联在男性中比女性更强[38]。相对于全身肥胖，腹部肥胖可能在结直肠癌的发生发展中起到更为重要作用。最近的荟萃分析研究了腹型肥胖[以腰围（waist circumference, WC）和腰臀比（waist-to-hip ratio, WHR）来衡量]与结直肠癌之间的关联，结果表明相对于较低的WC和WHR，较高WC和WHR者结直肠癌发病风险分别增加42%和39%[39]。一项纳入了58 667名绝经后妇女的队列研究表明，减肥可使结直肠癌发

病风险降低21%[40]。

与过多的能量摄入、超重和肥胖相反，体育锻炼与结直肠癌发病风险成反比[22,41]。来自美国和欧洲地区大队列的数据表明，与低水平的休闲体育活动（P_{10}）相比，高水平的体育活动者（P_{90}）结肠癌发病风险降低16%，直肠癌发病风险降低13%[42]。与体力活动可降低结直肠癌发病风险相反，久坐行为可增加多种癌症的发病风险，包括结直肠癌和晚期腺瘤[43]。久坐时间每天每增加2 h，结直肠癌发病风险将增加8%（95%*CI*：4%～11%）[44]。

3. 非甾体类抗炎药物：包括阿司匹林在内的非甾体类抗炎药物（non-steroidal anti-inflammatory drugs，NSAIDs）是公认的结直肠癌保护因素，可作为结直肠癌化学预防手段，研究认为NSAIDs主要通过抑制COX-2来预防结直肠癌[45]。荟萃分析表明，服用阿司匹林与结直肠癌发病风险之间呈负相关（*RR*＝0.73，95%*CI*：0.67～0.79），且长期服用保护性更加明显[46-47]。除阿司匹林外，服用其他NSAIDs药物可使＞40岁人群的结直肠癌发病风险降低26%（*OR*＝0.74，95%*CI*：0.67～0.81）[48]。

4. 微生物：随着肠道微生物研究的进展，越来越多证据表明肠道微生物失调与结直肠癌发生密切相关。最初，通过对粪便进行培养，研究者发现结直肠癌高危人群和低危人群肠道微生物组成不同[49]。对来自澳大利亚、法国、中国、美国、德国、意大利和日本的386例病例和382例对照的宏基因组数据进行Meta分析，发现了在结直肠癌病例与对照组中差异表达最显著的29个核心物种，包括梭杆菌、卟啉单胞菌、微单胞菌、消化道链球菌等，均在结直肠癌患者中显著富集[50]。在所有肠道微生物中，具核梭杆菌与结直肠癌发生发展的关联比较明确，多项研究中都发现结直肠癌患者粪便及肠癌组织中具核梭杆菌显著聚集[51]，功能学研究表明具核梭杆菌可通过促进肠道炎性微环境而有助于结直肠癌的发生[52-53]。此外，还有研究表明，幽门螺杆菌、溶血链球菌感染亦可能是肠癌的危险因素，但上述关联还有待进一步证实[54-55]。

5. 其他环境因素：环境中的苯、有机氯等污染物也会影响结直肠癌的发生。2018年，对4个北欧国家进行的大型病例对照研究发现，工作场所苯暴露可使结直肠癌发病风险升高12%，且存在一定的剂量反应关系[56]。此外，结直肠癌发病风险的升高可能与血清中多氯联苯的浓度升高有关[57]。

二、遗传因素与结直肠癌的发病风险的关联

早期的结直肠癌遗传易感性研究基于已知的病理生理基础，选择可能与结直肠癌相关的基因作为候选基因，通过比较病例及对照中候选基因中的遗传变异如单核苷酸多态性（single nucleotide polymorphism，SNP），分析结直肠癌的遗传易感性基础[58]。在这一时期，结直肠癌易感性的研究重点多集中于DNA错配修复、WNT/β-catenin、MYC、P_{53}等原癌、抑癌信号通路上的遗传变异[59-62]。然而候选基因策略仅从既定的单个或多个SNP出发，难以全面揭示结直肠癌的遗传背景，遗漏了大量的致病性遗传信息。

随着芯片技术的发展，研究者得以同时检测基因组中数以百万计的遗传标记（主要为SNP），并进行全基因组关联研究分析（Genome-wide association study，GWAS）[63]。目前，GWAS已确定了50余个与结直肠癌发病风险有关的候选基因座及100个左右的遗传变异[64-66]。继早期基于欧美人群的GWAS研究发现了rs6983267、rs10505477、rs7014346、rs719725、rs4939827、rs4779584、rs16892766、rs10795668、rs3802842、rs1957636、rs4813802等经典结直肠癌位点后，基于欧美人群的GWAS的荟萃分析，进一步确证了rs36053993、rs34612342、rs12953717、rs4464148、rs10505477、rs961253、rs16892766、rs10795668、rs3802842、rs355527、rs1862748、rs7259371、rs2736100、rs1800469，14个独立变体与结直肠癌发病风险高度相关[67]。最近基于亚洲结直肠癌协作组的大规模GWAS研究也在前期发掘的rs647161、rs2423279、rs10774214、rs4711689、rs4919687、rs11064437、rs2450115、rs6469656、rs7229639、rs58920878、rs12953717、rs4464148、rs4939827位点的基础之上[68-70]，进一步揭示出rs7542665、rs201395236、rs7606562、rs113569514、rs12659017、rs3830041、rs6584283、rs77969132、rs2730985、rs1886450、rs4341754、rs1078643、rs67052019、rs60911071、rs62558833、rs11108175、rs9634162等新的易感性位点，且进一步证实了之前与欧美人群结直肠癌发病风险相关的大多数位点也与东亚人群的肠癌风险有关[71-72]。为了最大化利用GWAS挖掘出来的遗传位点，研究者利用多个与结直肠癌相关的SNP构建了多基因风险评分（polygenic risk score，PRS），并以此来评估不同遗传背景人群的结直肠癌发病风险。Frampton等[73]利用37个高加索人群结直肠癌易感性位点建立了PRS，且发现最高1% PRS携带者的结直肠癌发病风险为一般人群的2.9倍。倘若人群中所有结直肠癌易感性位点已知的话，最高1% PRS携带者的肠癌发病风险为一般人群的7.7倍。Hsu等[74]的研究也证实了基于27个SNP的PRS可用于高加索人群的结直肠癌发病风险分层，且在基于肿瘤家族史的风险预测模型中加入PRS后，该模型在男性中的预测精确性提高8%，女性中的预测精确性提高4%。Weigl等[75]利用53个SNP构建的PRS被证实与德国人结直肠癌发病风险显著相关，且最高10% PRS携带者的结直肠癌发病风险为最低10% PRS携带者的3倍。

GWAS研究发现的结直肠癌相关的SNP位点大多位于基因的非编码区，如何从中找到真正与疾病相关的SNP，并从生物学上诠释其功能及其与疾病的关系是后GWAS时代的重大挑战之一。据评估，结直肠癌的遗传度是12%～35%[4]，但是GWAS中达到统计学显著的SNP能解释的遗传度相当有限，相当一部分的遗传位点亟待发现，尤其是一些高外显度的低频编码变异。后基因组时代，利用多组学手段尤其是全转录组关联研究（transcriptome-wide association studies，TWAS）成为寻找“消失的遗传变异”的新的研究策略。TWAS可以围绕GWAS基因座的精细定位（fine-mapping）促进功能候选基因和其他独立风险变体的检测，以发现最终的致病SNP[76-77]。研究表明，基于先前GWAS研究发现的21个结

直肠癌易感区域（包括29个SNP）进行精细定位，发现1q41（rs12759486）、19q13.1（rs7252505）与结直肠癌发病风险高度相关且具有统计学意义（$P<0.000\ 6$），在非洲裔美国人中，这两个新风险SNP对结直肠癌遗传力的贡献度约为1.5%[78]。大型病例-对照研究在GWAS识别的10q22.3区域进行了精细定位分析，识别出rs12263636、rs3740253和rs7071351 3个遗传变异，可影响RPS24基因的表达并与结直肠癌发病风险显著相关[79]。基于The Hispanic Colorectal Cancer Study与The Multiethnic cohort study数据的精细定位分析发现了rs7528276、rs1367374、rs142319636、rs143046984、rs185423955、rs60892987等结直肠癌发病风险位点[80]。

此外，高通量测序技术也为后GWAS时代注入了新的活力。最近的全基因组测序（Whole genome sequencing，WGS）与全外显子测序（Whole exome sequencing，WES）已经确定多个结直肠癌易感基因与变异位点，如rs112298707（DDX20）、rs68264412（ZFYVE26）、rs46509382（PIK3R3）、rs35911730（SLC26A8）、rs145156750（ZEB2）、rs95952304（TP53INP1）、rs219249005（SLC11A1）、rs151827481（LRBA）、rs37439069（CEBPZ）、rs67630823（ETAA1）、rs52474994（SEMA3G）、rs50325883（IFRD2）、rs187541196（FAT1）等[81]。最新的一项对结直肠癌的WGS与GWAS研究所进行的荟萃分析，确定了30个新的结直肠癌发病风险位点，包括常见变异rs12144319（1p32.3）、rs983402（2q33.1）、rs9271695（6p21.32）、rs7333607（13q13.3）、rs56324967（15q22.33）、rs1391441（15q22.33），低频变异rs72942485（3q13.2），及首次发现的5q21.1染色体处的罕见变异rs145364999[65]。近期的功能基因组学研究基于高通量RNA干扰技术筛选出位于12q13.12区域的基因*ATF1*是结直肠癌的关键驱动因素，并通过精细定位分析发现了rs61926301和rs7959129两个可增加结直肠癌发病风险的变异位点[82]。

三、基因-环境交互作用与结直肠癌的发病风险

结直肠癌的风险既取决于环境因素和遗传因素，还受到基因-环境交互作用的调控[83]。有关结直肠癌的基因-环境交互作用研究主要集中在前期已经确证的结直肠癌相关的环境危险因素，如饮酒、红肉及加工肉、阿司匹林等与遗传因素的交互作用上。基于20篇有关结直肠癌候选基因研究的荟萃分析确定了5种经多重比较调整后仍有意义的（$P<0.05$）基因-环境交互作用，即：N-乙酰转移酶2（NAT2）和加工肉摄入量、NAT2和红肉摄入量、rs16892766（8q23.3）和蔬菜消耗量、SHMT1 C1420T多态性和叶酸摄入量、rs6983267（8q24）和阿司匹林使用。研究中，对环境暴露与遗传变异之间相互作用的观察证据强度进行了观察评分，并基于主要环境效应和主要遗传效应的证据强度（1＝强，2＝中度，3＝弱）建立了相互作用的先验得分。根据观察与先验评分，发现了rs6983267（8q24）与阿司匹林使用之间的相互作用具有中等的总体可信评分和主要的遗传效应（$P=7.45\times10^{-13}$）[84]。有研究表明，经常使用阿司匹林或非甾体抗炎药与降低结肠癌的风险有关（$OR=0.69$，95%CI：0.64～0.74），而这种关联与12p12.3上的SNP rs2965667高度相关[85]。除了单个遗传和环境因素的交互作用与结直肠癌的关联，近期的研究还进一步探讨了遗传评分与生活方式评分的交互作用对结直肠癌发病风险的影响。Jeon等[86]的研究表明，基于19个生活及环境因素的环境风险评分与63个SNP的遗传风险评分建立模型，将PRS与生活方式评分结合起来可显著提高结直肠癌的风险分层作用。模型对男性及女性结直肠癌发病风险预测的AUC（ROC曲线下面积）分别为0.63和0.62。对于无结直肠癌家族史者，目前平均推荐筛查年龄为50岁。以此风险作为筛查阈值，利用环境风险评分与遗传风险评分进一步细分后发现，最低10%风险的个体，男性适宜的筛查年龄为56岁，女性为64岁；而最高10%风险的个体，男性适宜的筛查年龄为44岁，女性为50岁。对于最高1% PRS携带者，最高1%健康生活方式评分相对于最低1%生活方式评分可使50岁人群10年结直肠癌发病风险降低约90%。

目前，基因-环境交互作用对结直肠癌发病风险的影响仍然处于研究中，需要进行大样本和更进一步的研究，以确定可能对公共卫生产生重要影响的环境-基因交互作用。

四、小结

结直肠癌是一种复杂性疾病，除受环境因素影响外，也受到遗传因素的影响，同时基因-环境交互作用也在结直肠癌的发生发展中起着重要作用。多种饮食相关因素以及生活方式因素都与结直肠癌发病风险有较强的关联。在有关结直肠癌的遗传因素研究中，由于测序技术的不断发展，先后经历了候选基因策略、GWAS以及后GWAS时代，这将使人们在不断研究发现新的结直肠癌发病风险相关的SNP基础上，进一步筛选并确定真正与结直肠癌相关的基因与遗传变异，也有助于人们更进一步了解结直肠癌分子流行病学方面的病因，并综合遗传与环境因素构建更为完善的预测模型与干预方案，最终实现降低结直肠癌疾病负担的目标。

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