

早发性结直肠癌临床研究进展

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摘要

近年来, 早发性结直肠癌(early-onset colorectal cancer, EOCRC)的发病率逐年上升。虽然目前其发病机制尚未完全明确, 但与其相关潜在的危险因素, 例如生活方式、饮食习惯、遗传易感性及肠道菌群的影响等逐渐被各项研究报道。本文通过回顾国内外相关文献报道, 对EOCRC的相关危险因素、预防做一综述, 以提高人群对于EOCRC的预防意识, 从而降低疾病的发生率。

关键词

早发性结直肠癌, 危险因素, 预防, 研究进展

Clinical Research Progress of Early-Onset Colorectal Cancer

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Abstract

In recent years, the incidence rate of early-onset colorectal cancer (EOCRC) has increased year by year. Although its pathogenesis is not yet fully pinpointed, potential risk factors related to it, such as lifestyle, dietary habits, genetic susceptibility, and the influence of gut microbiota, have gradually been reported in various studies. This article reviews relevant literature reports at home and

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abroad to provide a review of the risk factors and prevention of EOCRC, in order to enhance the population's awareness of EOCRC prevention, and thereby reduce the incidence of the disease.

Keywords

Early-Onset Colorectal Cancer, Risk Factors, Prevention, Research Progress

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1. 引言

结直肠癌是常见的消化道恶性肿瘤之一，据文献报道，结直肠癌的发病率位居第三，且死亡率位居第二[1]。由于结直肠癌的高发病率和高死亡率，研究者们针对其进行了较为全面的研究，在发达国家，其发病率及死亡率趋于稳定甚至有下降趋势[2] [3]，这可能与发达国家通常对 50 岁以上的平均风险人群实行了结直肠癌的筛查有关[4] [5]。但值得注意的是，多项关于结直肠癌发病率的研究中指出：虽然 50 岁以上的人群，结直肠癌的发病率有所下降，但 50 岁以下的年轻患者结直肠癌发病率在逐渐上升[6]-[9]。EOCRC 的定义是 50 岁以下个体发生的结直肠癌。目前尚无报道明确指出 EOCRC 的发病原因及机制，不过与其发生的危险因素逐渐被发现，因此本文从 EOCRC 的危险因素及预防的角度做一综述，以期提高人群对于 EOCRC 的认识与预防意识。

2. EOCRC 发生的相关危险因素

2.1. 肥胖及较高的体重指数

在既往的报道中，人群的体重指数(Body mass index, BMI)升高与 EOCRC 的发生有着密切关系。Liu 等人[10]在其研究中对 85,256 名入组时健康的受试者进行长期随访，结果显示：BMI 每增加 5 个单位，患 EOCRC 的风险便提高 20%。Sanford NN 等人[11]通过研究肥胖症与结直肠癌发生之间的关系，发现 BMI ≥ 30 kg/m² 与年龄 < 50 岁存在交互，即年轻的肥胖人群更容易发生 EOCRC，而老年人群的 BMI 似乎与结直肠癌的发生无明显的关联。同样的，Li 等人[12]的研究中同样发现 BMI ≥ 30 kg/m² 与 EOCRC 的发生风险增加密切相关。甚至在 Murphy CC 等人[13]的研究中指出，孕产妇的肥胖及高 BMI 也会增加后代 EOCRC 的风险。此外，几项关于 BMI 与 EOCRC 关联的 meta 分析[14]-[16]同样显示：肥胖是 EOCRC 发生的一个重要危险因素，年轻人群的 BMI 上升可能会导致 EOCRC 发病率的上升，BMI 每增加 5 kg/m²，男性和女性患结直肠癌癌症的总体风险分别高 13% (RR: 1.13, 95% CI: 1.08~1.19)、17% (RR: 1.17, 95% CI: 1.09~1.25)。总之，早期身体肥胖可能会影响日后患结直肠癌癌症的风险。应强调预防年轻人的超重和肥胖，以预防因过度肥胖而导致的早发性结肠癌癌症。因此，可以认为较高的 BMI 是 EOCRC 发生的危险因素之一。

2.2. 不良生活方式

人群的生活方式也影响着 EOCRC 的发生率。在一项病例对照研究中指出：久坐时间 > 10 小时/天与 EOCRC 的风险有关[17]；Nguyen LH 等人[18]同样报道，久坐不动与 EOCRC 的风险增加有关，尤其是直肠更容易受累，这提示着不活跃的生活方式是“存在危险的”。精神心理压力的增大在当今社会是一

个普遍现象, Kikuchi N [19]等人的一项大规模前瞻性队列研究中发现, 常常感知到压力的人群发生 EOCRC 的风险显著提升, 尤其是与直肠癌的发生更加密切; Zhang 等人[20]的研究发现孕产妇压力增大同样会增加后代 EOCRC 的风险。饮酒已经被证实与 EOCRC 的发生有关, Jin 等人[21]在其研究中发现, 饮酒的量和饮酒的频率与 EOCRC 的发生密切相关, 与轻度饮酒者相比, 中度饮酒者和重度饮酒者发生 EOCRC 的风险增加[(HR: 1.09, 95% CI: 1.02~1.16)和(HR: 1.20, 95% CI: 1.11~1.29)]; 与非饮酒者相比, 饮酒频率为 1~2 天/周、3~4 天/周和 ≥ 5 天/周的风险分别增加 7%、14%、27%。Hur J 等人[22]针对年轻人群开展的前瞻性队列研究结果同样显示: 年轻人群的大量饮酒会增加 EOCRC 的发病率。吸烟对于 EOCRC 的发生是否有关, 目前似乎还没有定论, Khan NA 等人([23], p. 1)开展了一项单中心病例对照研究, 他们在单因素分析中发现吸烟具有统计学意义, 而在多因素分析中吸烟失去了显著性; Kim NH 等人[24]将研究人群以 10 岁为一组进行分组, 最终结果显示吸烟仅在 30~39 岁这一组中是 EORCR 的危险因素; Schumacher AJ 等人[25]的病例对照研究中发现, 肥胖会增加 EOCRC 的风险, 而吸烟似乎并不增加; O'Sullivan DE 等人([26], p. 1)认为吸烟可能是一种潜在的危险因素, 但相关性并无显著性(RR: 1.35, 95% CI: 0.81~2.25)。

2.3. 饮食习惯

Rosato V 等人[27]的通过一项病例对照研究评估饮食习惯对 EOCRC 的影响, 研究结果显示, 加工肉类的过量摄入会使 EOCRC 的风险明显提高, 而较多的蔬菜及水果的摄入会降低其发生的风险; Chapelle N 等人[28]同样发现了过多食用加工肉类对于 EOCRC 的风险。因为红肉在加工过程中会产生致癌物, 例如: 杂环胺, 多环芳烃等, 其次, 过多的食用红肉会导致致癌的 N-亚硝基化合物和脂质过氧化物的形成, 从而引起 EOCRC 的发生[29]。国外有研究者提出“西方饮食”(即大量摄入红肉、加工肉类、含糖饮料、精制谷物、甜点和土豆等低纤维饮食方式)和“健康饮食/地中海饮食”(即富含水果、蔬菜、谷物、豆类等高纤维饮食方式) ([30], p. 1), 在后续的多项研究中发现, 西方饮食模式是 EOCRC 的危险因素, 而健康饮食模式是 EOCRC 的保护因素([23], p. 2) [31]-[33], 因此有学者指出采取健康饮食模式可以降低 EOCRC 的发生风险[34]。除了蔬菜、水果等高纤维食物等, 牛奶及乳制品似乎是 EOCRC 的保护因素 [35]-[38], 因为钙离子可以与胆汁酸和脂肪酸结合, 减少它们对肠上皮的损伤[39], 并且钙离子作为细胞信号通路的一环, 可以促进细胞的分化和凋亡[40]。此外, 近些年有研究发现 EOCRC 的癌前病变与含硫微生物饮食相关[41], 微生物可将硫转化为有致癌性的硫化氢, 从而引起 EOCRC 的癌前病变。

2.4. 遗传因素

与晚发性结直肠癌病例类似, 结直肠癌的家族史仍然是 EOCRC 的重要危险因素, (RR: 4.21, 95% CI: 2.61~6.79) ([26], p. 2)。但有 20% 的 EOCRC 患者存在与肿瘤相关的种系变异[42], 在 EOCRC 的患者中, 最常见的种系变异是 Lynch 综合征相关基因(MLH1、MSH2、EPCAM、MSH6 和 PMS2) [43]。与没有遗传因素相关的结直肠癌相比, Lynch 综合征相关 EOCRC 常呈现出更年轻、发展更迅速的特点[44] [45], 因此对于 EOCRC 的患者推荐使用多基因癌症组合进行种系检测。

2.5. 其他疾病的影响

其他疾病对于 EOCRC 的发生也有着一定的影响。Ali 等人[46]的一项队列研究中发现, 50 岁之前诊断为糖尿病会增加 1.9 倍 EOCRC 的风险, 而在有结直肠癌家族史的病例中, 这一风险甚至提高到了 6.9 倍。Kim 等人[47]的研究同样证实了这一点。代谢综合征(Metabolic Syndrome, MetS)是一组以肥胖, 高血糖, 高血脂以高血压等聚集发病的一组临床症候群, Ye 等人([48], p. 1)报道出代谢综合征会增加 EOCRC 的风险(OR: 1.34, 95% CI: 1.25~1.44); Chen 等人[49]在其研究中同样地发现了 MS 对 EOCRC 的影响(OR:

1.25, 95% CI: 1.09~1.43), 并且于无代谢综合征的患者相比, 代谢综合征包含的疾病越多, 其风险便越大, 患有 1 种、2 种以及 3 种以上的代谢综合征的患者发生 EOCRC 的风险分别增加 9%、12%、31%。Jin 等人[50]的研究也证实了这一点, 当患者存在 5 种 Mets 时, 其发生 EOCRC 的风险会增加至 50%。此外, 在一些探究 EOCRC 发生的危险因素的研究中也发现了炎症性肠病也会增加其发生的风险([48], p. 2) [51] [52]。这些研究证实了其他疾病与 EOCRC 发生的联系。

2.6. 肠道菌群的影响

肠道菌群与结直肠癌的相互作用是近年来研究的热点, 肠道菌群失调的特征是细菌种类的改变, 导致有益细菌和致病细菌之间的不平衡[53] [54]。肠道微生物群与正常宿主生理学的许多方面密切相关, 从营养状况到生物行为, 微生物们都直接参与肠道粘膜稳态的调节, 肠上皮防御屏障功能的维持以及肠道的免疫功能[55]-[57]。一项有关 EOCRC 患者肠道菌群分析的研究中发现[58], 30% 的 EOCRC 患者肿瘤组织中存在双歧杆菌, 且双歧杆菌的数量与印戒细胞的数量呈正相关, 这表明双歧杆菌可能在肿瘤发展中发挥作用。另一项分析 EOCRC 患者肠道菌群的研究中发现[59], EOCRC 患者粪便中肠道菌群多样性显著低于同年龄阶段的对照组人群, 且 EOCRC 患者的肠道细菌的 DNA 结合及 DNA 合成途径过于活跃, 这就导致其增殖能力及侵袭力的增加, 因此, EOCRC 患者的肠道菌群常常表现为更易恶性进展的代谢状态, 这可能与临床上 EOCRC 的患者疾病进展较快相关。

2.7. 药物的影响

一项大规模的病例对照研究中[60]纳入了 800 多种药物来评估药物制剂是否会增加 EOCRC 的风险, 结果显示与 EOCRC 发生风险持续呈正相关的药物包括了 β 受体阻滞剂和缬草(一种作用于神经系统的中草药)。Jiang 等人[61]在研究中发现, 长期、反复的使用抗生素与 EOCRC 风险增加有关, 而抗生素的反复使用甚至滥用引起 EOCRC 风险增加的机制是影响了肠道的微生物而实现。Jones 等人[62]发现阿司匹林的使用能够降低 EOCRC 的风险, 据分析是因为阿司匹林降低了炎症因子对 EOCRC 的促进作用。

3. EOCRC 的危险信号体征与临床表现

据报道, 大多数 EOCRC 病例都出现过危险信号及表现。最常见的信号是黑便或便血, 其次是腹痛、排便习惯的改变(便秘或腹泻)、不明原因的体重减轻和贫血[63] [64] ([65], p. 1) [66] [67] ([68], p. 1) [69]。Syed 等人[70]构建了危险信号的出现于 EOCRC 发生的风险预测模型, 证实了上述危险信号的出现的确与 EOCRC 发生风险增加有关。此外, Demb 等人[71]的研究结果显示, 出现便血和缺铁性贫血与 EOCRC 发生风险增加 10 余倍有关(HR: 10.81, 95% CI: 8.15~14.33)。但往往 EOCRC 的诊断会延迟, 根据几项医疗中心相关研究表示([65], p. 2) ([68], p. 2) [72] [73]: EOCRC 患者从出现症状到确诊往往存在滞后性, 患者确诊时疾病大多已进展为 III 期或 IV 期, 关于这种情况的可能解释是: (1) 患者较为年轻且缺乏疾病风险意识; (2) 在出现症状后并未及时进行检查或没有条件进行检查; (3) 医务人员对于年轻患者的危险信号表现多倾向于良性疾病的表现。

4. EOCRC 的预防

EOCRC 的治疗与迟发性结直肠癌的治疗基本类似, 但因患病人群的特殊性以及疾病本身倾向于快速进展, 因此对于 EOCRC 的预防相比治疗更加重要。虽然目前对于 EOCRC 的具体发病原因和机制尚未完全清楚, 但与其相关的危险因素已经有了大量的报道, 对于遗传因素这种不可改变的因素而言, 及时的筛查便是预防的最佳手段。Gupta 等人[74]指出 40~49 岁的 EOCRC 病例中有 1/4 符合早期筛查的家族史标准, 如果进行早期筛查, 98% 符合家族史标准的病例可以更早诊断(甚至可能预防)。而对于其他可改变

的危险因素, 例如肥胖、不良生活方式、饮食习惯等, 普通人群可以通过调整生活习惯, 例如多参加体育活动, 避免久坐; 多食用蔬菜、水果、牛奶乳制品等方式来达到预防的效果([30], p. 2)。目前已有多项报道证明早期筛查对于降低结直肠癌的发病率和死亡率的有效性报道[75]-[80], 因此医疗机构可以通过开展 EOCRC 的知识宣传, 提高人群对 EOCRC 的认识, 并建议存在危险因素的风险人群进行早期筛查, 做到早发现、预防、早治疗。

5. 小结

近些年来, EOCRC 的发病率逐年上升, 给人群的健康带来了较大的威胁, 因而关于 EOCRC 的研究成为热点。尽管具体的致病原因尚未确定, 但重要的是能够发现 EOCRC 相关的危险因素, 例如: 生活方式、饮食习惯等。未来有关于 EOCRC 的研究应侧重于进一步发现明确的病因、发病机制、潜在的危险因素以及适用于 EOCRC 的有效治疗, 从而制定更完善、更健全、更容易实施的预防策略以及更高效、更安全的治疗方案, 提高疾病的早期诊断与发现率, 改善治疗后的预后与生存治疗, 切实地降低 EOCRC 对人群的影响。

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