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· 文献综述 ·

## 年轻人结直肠癌的诊疗进展

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### 摘要

结直肠癌是最常见的恶性肿瘤之一, 其发病率和病死率均居恶性肿瘤前五位。近年来, 越来越多的报道指出结直肠癌发病呈现年轻化趋势, 且这部分患者的分期更晚、预后更差, 然而目前对年轻结直肠癌的定义、危险因素、临床特点、治疗方式及预后认识仍不足。现笔者结合国内外最新研究就上述几个方面作一综述, 以供临床参考。

### 关键词

结直肠肿瘤; 青年人; 危险因素; 预后; 综述文献  
中图分类号: R735.3

## Advance in diagnosis and treatment of young-onset colorectal cancer

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### Abstract

Colorectal cancer is one of the most common malignant tumors, with morbidity and mortality ranking on the top five among all cancers. In recent years, an increasing number of reports indicate that the incidence of colorectal cancer is on the rise in younger population, with more advanced stage and worse prognosis. However, the understandings on the definition, risk factors, clinical features, treatment methods and prognosis of the young-onset colorectal cancer are still limited. Here, the authors address the above aspects with review of the latest research at home and abroad to provide a reference for clinical practice.

### Key words

Colorectal Neoplasms; Young Adult; Risk Factors; Prognosis; Review  
CLC number: R735.3

结直肠癌是世界上最常见的恶性肿瘤之一。在我国, 结直肠癌位于男性恶性肿瘤发病率的第四位, 女性恶性肿瘤发病率的第3位, 并且在病死率最高的前十位癌症中, 结直肠癌分别位于男性和女性的第5位和第4位<sup>[1]</sup>。近年来, 尽管医学诊

疗技术得到飞速发展, 研究<sup>[2]</sup>也证实结直肠癌的发病率和病死率在西方国家呈下降趋势, 但在亚洲国家中, 结直肠癌的发病率和病死率则呈上升趋势, 在我国尤为明显<sup>[1, 3]</sup>。结直肠癌好发于中老年人, 有研究<sup>[4]</sup>报道超过90%的结直肠癌患者发生于50岁以上, 然而, 最近越来越多的研究<sup>[5-8]</sup>指出年轻结直肠癌的发病率明显增高, 且与年老患者相比分期更晚、预后更差。有研究<sup>[8]</sup>估计, 到2030年, 20~34岁的结肠癌和直肠癌的发病率将分别

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上升90.0%和124.2%，35~49岁的患者分别上升27.7%和46.0%。届时，<50岁的结肠癌患者和直肠癌患者将分别占有所有结直肠癌患者的10.9%和22.9%，而在2010年这一比例仅为4.8%和9.5%。因此，对年轻结直肠癌的定义、危险因素、临床特点、诊疗方法及其预后等研究进展作一综述，进而指导临床医师提高对年轻结直肠癌的认识，做到早诊断、早治疗具有重要意义。

## 1 年轻人结直肠癌的定义

目前年轻人结直肠癌的定义尚无统一标准，对其年龄划定也各自不一，有研究<sup>[9-10]</sup>划定为<40岁，有研究<sup>[11]</sup>划定为<45岁，然而大部分文献<sup>[5, 12-15]</sup>将其定为<50岁。结合目前美国预防服务工作组（United States Preventative Services Task Force, USPSTF）推荐结直肠癌的筛查从50岁开始<sup>[16]</sup>，且50岁以下和50岁以上结直肠癌的发病趋势、临床特征及其预后被越来越多的文献报道存在明显差异，故本次叙述的年轻人结直肠癌为年龄<50岁的结直肠癌。

## 2 发病的危险因素

结直肠癌是由多种因素共同作用的结果<sup>[17]</sup>。除了年龄和性别外，大肠癌家族史<sup>[18]</sup>、炎症性肠病<sup>[19]</sup>、吸烟<sup>[20]</sup>、酗酒<sup>[21]</sup>、食用过多红肉<sup>[22]</sup>、肥胖<sup>[23]</sup>、糖尿病<sup>[24]</sup>等均已被证明和结直肠癌发病有关，其中一级亲属中患有结直肠癌或既往有炎症性肠病的患者与结直肠癌发病率的增加最为密切。近来有报道<sup>[25-26]</sup>幽门螺杆菌、梭杆菌属和其他潜在传染原感染可能与结直肠癌风险增加有关。而对于年轻结直肠癌发病率日益增加的原因各报道意见不一，我们现将其总结如下。

### 2.1 肥胖

肥胖被认为是结直肠癌发病的高危因素<sup>[23, 27]</sup>。美国近30年来所有年龄段人群肥胖的患病率均明显增加<sup>[28-29]</sup>，有学者<sup>[30]</sup>认为这可能是导致年轻结直肠癌发病率呈总体上升趋势的原因之一。而在中国，随着生活水平的提高，成人和儿童中肥胖和超重的比例也日益上升<sup>[31]</sup>。研究<sup>[32]</sup>指出儿童肥胖和超重的比例由1985年的<3%升至2010年的20%，而

成人这一比例则于2010年达到了42.6%<sup>[33]</sup>，这也许能部分解释中国的结直肠癌总体发病率不降反升的原因。

### 2.2 食用过多红肉

红肉中含有较高的饱和脂肪酸，食用过多会增加结直肠癌发病的风险，世界卫生组织国际癌症研究机构已将其纳入2A类致癌物清单中。有研究<sup>[30, 34]</sup>指出从1977—1996年，在青少年（12~18岁）和年轻人（19~29岁）中，来自汉堡之类的快餐平均能量摄入量增加了30%，而来自牛奶的能量摄入比例下降了42%，这种饮食的变化可能是导致年轻结直肠癌发病率增加的潜在原因。

### 2.3 遗传因素

据估计，年轻结直肠癌患者中有大约10%是和遗传因素有关的<sup>[12]</sup>。当新诊断年轻结直肠癌时，应首先考虑其是否患有遗传性疾病，如家族性腺瘤性息肉病，林奇综合征（Lynch syndrome, LS），MUTYH相关性息肉病以及不常见的Peutz-Jeghers综合征和幼年性息肉病等。目前指南不推荐年龄<50岁且无危险因素的成年人接受常规结直肠癌筛查，而高危人群（即有家族性息肉病史，遗传性非息肉病性结直肠癌或溃疡性结肠炎病史）则建议在50岁之前开始筛查<sup>[8]</sup>。

### 2.4 吸烟、饮酒

吸烟与结直肠癌的亚型有关，特别是在有微卫星不稳定性（microsatellite instability, MSI）的散发性老年人结直肠癌患者中更明显<sup>[35]</sup>。然而，吸烟引起结直肠癌通常需要几十年的诱导，这个一个长期的过程，并且有研究<sup>[36]</sup>表明，年轻人的吸烟率正在下降，吸烟不太可能是年轻结直肠癌发病率增加的原因。另外，有研究<sup>[37]</sup>指出，饮酒对于45岁以下且有结直肠癌家族史的人群是一个高危因素。

## 3 年轻人结直肠癌的临床特点

### 3.1 临床表现

年轻结直肠癌患者的临床表现与年老患者相似，但通常不典型。O'Connell等<sup>[38]</sup>分析指出绝大多数的年轻结直肠癌患者在就诊时已有临床症状，极少数在体检时发现，最常见的症状为腹痛（55%）和便血（46%），其次是体质量减轻（35%）和排

便习惯改变(32%);直肠和乙状结肠是年轻结直肠癌患者最常见的发生部位,占大肠癌的54%,其次是升结肠(22%),降结肠(13%),横结肠(11%)。Siegel等<sup>[30]</sup>也指出,86%的年轻结直肠癌患者在诊断时已有症状,同时指出50岁以下结直肠癌患者增加的原因主要是由于左侧大肠癌特别是直肠癌的增加造成的。另有研究<sup>[39]</sup>指出21%的年轻结直肠癌患者在得到确诊时症状已经超过6个月。因此,对于有家族史或癌前病变的年轻人,因腹痛、便血、排便习惯和大便性状改变就诊时,临床医生要提高警惕,应有对结直肠癌的鉴别诊断,以减少误诊和漏诊。

### 3.2 临床分期

年轻结直肠癌患者临床分期通常比年老患者更晚<sup>[5-8, 13]</sup>。来自SEER(Surveillance, Epidemiology and End Results)分期数据显示,2000—2009年,50岁以下的结直肠癌患者,TNM分期3期或4期的占67%,局限于原发部位的占30%,扩散到肠系膜淋巴结的占40%,有远处转移的占27%;然而,50岁以上患者的这一比例依次为56%、39%、37%和19%<sup>[40]</sup>。众多学者<sup>[9, 36, 39]</sup>将这一结果归因为诊断的延误。而诊断延误往往是由患者和医生共同造成的<sup>[41]</sup>。有研究<sup>[38]</sup>指出,由患者和医生造成的诊断延误平均时间分别是6.2个月和3~6个月,主要是由于医务人员的疏忽或认识不足,导致很多年轻人的症状被误诊为是痔等良性疾病。年轻医师对于50岁以下的结直肠癌做出精准的诊断是有难度的<sup>[42]</sup>。因此我们在推荐结直肠癌筛查年龄从50岁开始时也应该提高对50岁以下结直肠癌的认识,75%的直肠癌是在直肠指诊时被发现的,笔者认为直肠指诊和肠镜检查是减少年轻结直肠癌误诊和漏诊的保证。另外,对于年轻结直肠癌分期较晚是否与其更具侵袭性的肿瘤生物学特性有关联目前还不确定<sup>[43]</sup>。

### 3.3 病理特点和分子生物学特点

年轻结直肠癌患者在肿瘤分化程度和组织学类型方面与年老患者有明显不同,年轻患者的肿瘤特征往往更具侵袭性<sup>[12]</sup>,黏液腺癌、印戒细胞癌和低分化腺癌的比例明显高于年老患者。有学者<sup>[44]</sup>发现,随着年龄的增加,结直肠癌患者中产生粘蛋白的肿瘤(包括印戒细胞癌和黏液腺癌)比例显著降低,年老患者的低分化腺癌比例较年

轻患者也低很多。O'Connell等<sup>[38]</sup>报道,年轻结直肠癌患者中黏液腺癌占21%,印戒细胞癌占3%,低分化腺癌占27%。

MSI代表细胞的“突变表型”,即具有MSI的肿瘤细胞倾向于多个基因的突变,尤其是具有重复DNA序列的突变。研究<sup>[45-46]</sup>表明,MSI可以导致多种下游细胞生长调控基因的改变,从而加速结直肠癌的进展。年轻结直肠癌患者的分子生物学与老年患者不同,他们具有高微卫星不稳定性(MSI-H)<sup>[47-48]</sup>。因此由于MSI-H的比例高,年轻结直肠癌患者病情进展得快,导致在初始诊断时就处于更晚期<sup>[49]</sup>。而MSI-H肿瘤的预后往往较好,这或许可以解释为什么处于同一分期的肿瘤,年轻结直肠癌患者比年老患者具有更高的生存率<sup>[38, 47]</sup>。

## 4 年轻结直肠癌的治疗及术后监测

年轻结直肠癌患者的治疗方式与年老患者相同,以外科手术为主<sup>[12]</sup>。美国国家综合癌症网络(National Comprehensive Cancer Network, NCCN)<sup>[50]</sup>建议,当结直肠癌得到诊断后,术前应检查胸部、腹部和骨盆的CT评估患者转移情况,以便对结直肠癌进行分期,同时检测患者血清癌胚抗原(carcinoembryonic antigen, CEA)水平,帮助指导治疗后的随访,年轻的结直肠癌患者还应进行MSI检测以评估LS的可能性。对于不伴遗传易感性的结直肠癌患者,不论年龄大小,手术切除都是主要的治疗方式。由于年轻患者对性功能、排便、泌尿等要求比较高,术者应在保证肿瘤根治性原则的前提下,最大限度的保留患者上述功能以提高生活质量。肠癌患者术后1年内复查肠镜,如果术前肠镜检查不全则时间调整为术后3~6个月以内,这些检查策略不因年龄而异<sup>[51-52]</sup>。由于直肠癌局部复发率高于结肠癌,所以在直肠癌术后的前两年需每3~6个月进行1次直肠超声或肠镜检查。

## 5 年轻人结直肠癌的预后

最新数据<sup>[53]</sup>显示我国结直肠癌的5年生存率男性为48.1%,女性为46.2%,然而关于年轻结直肠癌患者的预后一直意见不一<sup>[5, 9, 12, 15, 36, 49]</sup>。

Chung等<sup>[9]</sup>认为处于同一分期的年轻患者和年老患者相比较时,其生存率并无明显差异,并指出年龄<50岁并不是结直肠癌较差预后的标志,不应该消极的看待。同样地,Liang等<sup>[49]</sup>研究指出IV期的年轻结直肠癌患者存活时间明显长于老年患者,并且对126例患者分析得出肿瘤低分化、产生黏蛋白、CEA浓度高于3.5 ng/mL、IV期肿瘤、p53基因过度表达和结直肠癌缺失基因(deleted in colorectal cancer, DCC)基中的杂合性丢失(loss of heterozygosity, LOH)基因表达是预后不良的重要因素。Yang等<sup>[54]</sup>认为年轻结直肠癌患者发生异时性多原发结直肠癌的风险较高,但其生存率比年老患者好,因为他们接受根治性手术的比例较高且随访时间较长。然而,当单独研究直肠癌时发现,40岁以下患者的预后不佳,与老年患者相比术后转移率更高,总生存期更短<sup>[55]</sup>。有研究<sup>[56]</sup>发现50岁以下结直肠癌患者术后前20个月的生存率较低,但其后的生存率与50岁以上者相当。以上研究均需多中心、进一步的研究证实,不过对于年轻结直肠癌患者早发现、早诊断、早治疗仍是提高其生存率和生活质量的重要措施。

综上所述,随着结直肠癌的发病越来越年轻化,人们对年轻结直肠癌的认识也逐步深入。在精准治疗和个体化治疗日益发展的形势下,对于年轻结直肠癌如何准确地做出疾病诊断、合理地选择手术方式以及精准地确立术后需辅助治疗的人群等仍需多中心、大样本的随机对照研究获得高级别的循证医学证据。

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