·述评·

# 重视对早发性结直肠癌的认识

胡烨婷[1] 肖乾[1] 丁克峰[1,2] 郑树[1]
[1]浙江大学医学院附属第二医院大肠外科 恶性肿瘤预警与干预教育部重点实验室 浙江省恶性肿瘤临床医学研究中心，杭州 310009；[2]消化系统医药基础研究创新中心（教育部），杭州 310058
通信作者：丁克峰，Email：dingkefeng@zju.edu.cn

**【摘要】** 50岁以下人群中早发性结直肠癌（EOCRC）的发病率和死亡率呈上升趋势。尽管传统流行病学研究已经做了较为深入的研究，筛选出与EOCRC相关的环境因素，但对其病因、机制及治疗的认识还远远不够。因此，本文总结了EOCRC的当前研究进展，特别关注流行病学、筛查现状、临床症状和预后情况，为包括精准筛查在内的二级预防提供新依据，为改善EOCRC治疗提供诊疗新思路。

**【关键词】** 结直肠肿瘤，早发性； 流行病学； 筛查； 临床特征
**基金项目：**国家重点研发计划（2017YFC0908200）；浙江省重点研发计划项目“领雁”计划（2023C03049）

**Emphasis on awareness of early-onset colorectal cancer**

*Hu Yeting[1], Xiao Qian[1], Ding Kefeng[1,2], Zheng Shu[1]*
*[1]Department of Colorectal Surgery, the Second Affiliated Hospital, Zhejiang University School of Medicine; Key Laboratory of Cancer Prevention and Intervention, Ministry of Education; Zhejiang Provincial Clinical Medical Research Center for Malignant Tumors, Hangzhou 310009, China; [2]Center for Medical Research and Innovation in Digestive System Tumors, Ministry of Education, Hangzhou 310058, China*
*Corresponding author: Ding Kefeng, Email: dingkefeng@zju.edu.cn*

**【Abstract】** The incidence and mortality rates of early-onset colorectal cancer (EOCRC) among people under 50 years old are showing an upward trend. Although traditional epidemiological studies have conducted relatively deep research and screened out environmental factors related to EOCRC, our understanding of the causes, mechanisms, and treatment of this disease is still far from sufficient. In this review, we clarify the current progress of EOCRC, with a particular focus on epidemiology, screening status, clinical symptoms, and prognosis. This provides new evidence for secondary prevention, including precision screening, and offers new ideas for improving the diagnosis and treatment of EOCRC.

**【Key words】** Colorectal neoplasms, early-onset; Epidemiology; Screening; Clinical characteristics
**Fund programs:** National Key Research and Development Program of China (2017YFC0908200); Key Research and Development Program of Zhejiang (2023C03049)

结直肠癌（colorectal cancer，CRC）是消化系统最常见的恶性肿瘤之一，每年新增病例180万，发病率全球第3，死亡率排名第2位，2018年全球有超过88万人死亡[1]。根据国家癌症中心统计显示，我国CRC发病率高居第2位，死亡率第4位[2]。根据诊断年龄，50岁之前诊断的CRC称为早发性结直肠癌（early-onset colorectal cancer，EOCRC），超过50岁诊断的CRC称为晚发性结直肠癌（late-onset

**DOI：**10.3760/cma.j.cn441530-20240305-00086
**收稿日期** 2024-03-05 **本文编辑** 王静
**引用本文：**胡烨婷，肖乾，丁克峰，等. 重视对早发性结直肠癌的认识[J]. 中华胃肠外科杂志，2024，27(5)：430-435. DOI：10.3760/cma.j.cn441530-20240305-00086.

colorectal cancer，LOCRC）。EOCRC 是美国 50 岁以下人群中第二大常见癌症，也是导致癌症死亡的第三大原因[3]。全球范围内 EOCRC 的发病率和死亡率呈上升趋势，预计到 2030 年将增加 140% 以上，发病率与年龄呈负相关[4-9]。尽管缺乏完整的证据和严格的研究，但癌症相关的诱发因素已被证实与 EOCRC 有关（例如不良饮食、习惯久坐、吸烟和饮酒等）[3,7]。此外，EOCRC 被认为在流行病学、筛查特点、临床特征和诊疗情况方面与 LOCRC 具有显著不同的特征[10]。本文根据 EOCRC 流行病学特征、筛查及其临床特征以及诊治等情况进行评述，以期帮助大家更好地了解 EOCRC 的特征，进而促进有效的预防、早期发现和诊治策略的改进。

一、EOCRC 癌的流行病学特征

近几十年来，许多国家的男性和女性 EOCRC 发病率均呈上升趋势[7,11]。2008—2012 年间，新西兰 EOCRC 发病率的平均年变化百分比为 4.0%，加拿大和澳大利亚为 2.8%，美国为 2.2%[7]。在美国，EOCRC 发病率自 20 世纪 90 年代中期以来持续增加，每 10 万人中，EOCRC 发病率在 2000 年为 5.9 例，而 2017 年为 8.4 例[12]。1990—2016 年间，20~29 岁人群中 EOCRC 发病率（每 10 万人）从 0.8 例增加到 2.3 例，2006—2016 年间，30~39 岁人群中，从 2.8 例增加到 6.4 例，2016 年，每 10 万人中，从 15.5 例增加到 19.2 例。2004—2016 年间，20~29 岁人群中 EOCRC 发病率的年平均百分比变化为 7.9%，30~39 岁人群中为 4.9%，40~49 岁人群中为 1.6%[8]。综上，现在 EOCRC 对年轻人而言，是一个重大的癌症负担。

美国 EOCRC 发病率增加最初主要为直肠癌[12]。1980—2013 年间，20~39 岁人群直肠癌发病率为 3.2%；1991—2013 年间，40~49 岁人群的直肠癌发病率为 2.3%；而 1983 年，20~29 岁人群结肠癌发病率为 2.4%；1988—2013 年期间，30~39 岁年龄段结肠癌为 1.0%；1996—2013 年期间，40~49 岁年龄段结肠癌为 1.3%[8]。然而，自 2012 年以来，结肠和直肠的 EOCRC 发病率也出现了类似的增长，年百分比变化为 1.8%[1]。在欧洲，结肠癌 EOCRC 发病率的上升似乎比直肠癌更为突出[8]。

研究 EOCRC 潜在危险因素的流行病学调查大部分为病例对照研究[13-15]。病例对照研究中显示的潜在 EOCRC 危险因素包括男性[14]、种族（黑人和亚洲人种）[14]、CRC 家族史[14-15]、酒精[15]、体质量减轻≥5 kg（5 年内）[13]、加工肉类摄入量[15]和炎性肠病[14]。相反，服用阿司匹林[13]以及摄入更多的蔬菜[15]、柑橘类水果[15]、鱼和部分维生素[15]与降低 EOCRC 风险相关。在少数两项已发表的前瞻性研究中，久坐的生活方式（以看电视时间衡量）[16]和肥胖[17]与 EOCRC 的较高发病率有关。然而，肥胖与 EOCRC 之间虽然部分研究显示有正相关关系，但目前研究仍然未给出定论[17-18]。2021 年，利用 IBM MarketScan Commercial 数据库进行的另一项研究发现，代谢综合征与近端早发性结肠癌有关（aOR=1.37，95%CI：1.04~1.81），但与早发性远端结肠癌或直肠癌无关[19]。根据护士健康研究Ⅱ的最新研究表明，西方饮食与早发高危腺瘤的风险增加相关（aOR=1.67，95%CI：1.18~2.37），在远端结肠和直肠表现更为显著[20]。

二、EOCRC 的筛查进展

美国结直肠癌多社会工作组（US Multi-Society Task Force，USMSTF）建议，有 CRC 家族史、且一级亲属在 60 岁之前被诊断出的人群，从 40 岁开始或在亲属被诊断年龄前 10 年开始，每 5 年接受一次结肠镜检查[21]。2018 年，美国癌症协会（American Cancer Society，ACS）建议，从 45 岁开始对平均风险人群进行筛查，这是基于疾病负担、微观模拟模型的结果，以及对 45~49 岁成年人的筛查效果与老年人相似的合理预期做出的建议[22]。在 45~49 岁个体的全国代表性样本中，CRC 筛查率在 2018 年从 4.8% 上升至 12.0%，与 ACS 指南发布一致[23]。2021 年，美国预防服务工作组（US Preventive Services Task Force，USPSTF）指南在筛查起止年龄推荐中，也新增了对 45~49 岁人群进行筛查的 B 类建议[22]。以上建议主要基于 EOCRC 发病率和死亡率上升的模型研究，该研究预测，早期开始筛查将避免每 1 000 名在 45 岁（而不是 50 岁）开始定期筛查的人中额外增加 1 例 CRC 死亡[24]。

尽管基于粪便隐血的检测和结肠镜检查的筛查可能对 EOCRC 的二级预防有用，但筛查方法以及对平均风险或高风险人群开始筛查的建议年龄尚未达成广泛共识[25-27]。粪便免疫化学检测阳性人群若不进行后续结肠镜检查，其远端肠癌的发病和死亡风险会显著增加，50 岁以下人群风险增加更为显著[28]。最近一项基于 19 295 例患者的系统综述表明，早发性腺瘤的总体患病率为 11.0%（95%CI：8.5%~14.0%）[29]。一级亲属患有进展期腺

瘤会使终生患CRC的风险增加4倍[30-31]。因此指南建议，这些高危人群在40岁开始进行CRC筛查[21]。但是年轻人对这一建议的依从性很低[32]。提高进展期腺瘤及CRC家族史的年轻高危人群的风险意识，是改善这类高危人群筛查依从性并遏制EOCRC发病率上升的有效手段[33]。尽管理想情况下应根据每个人自身的风险量身定制筛查，但CRC筛查尚未采用个性化风险评估。对遗传基因多态性、生命早期暴露及其环境相互作用的评估，可能会提高早发CRC的筛查和早期检测的效率。另外一方面，尽管年轻人群的CRC发病率在增长，但年轻人群的肠癌发病率绝对值还是远低于老年人群的，那么目前的筛查方法是否适用于年轻人群，目前的证据还非常有限；对于年轻人群的筛查，采用风险评分进行高危人群的识别，可以减轻肠镜检查的负担，是比较推崇的一种筛查方式，但现有的肠癌风险预测模型还需进一步的优化，且需要本土数据的验证和完善，才能更好地转化应用。

三、EOCRC的临床特征

由于年轻患者肿瘤更具侵袭性以及患者和临床医生对症状的忽视，大多数EOCRC是由于体征和症状的出现而就诊的，并不是偶然或在筛查过程中发现的[34]；与LOCRC患者相比，EOCRC患者在就诊时分期更晚，Ⅲ~Ⅳ期比例高[35-37]；且EOCRC患者的诊断时间和症状持续时间显著长于LOCRC[37-39]。腹痛(46%)和直肠出血(47%)是EOCRC最常见症状，体质量减轻症状出现频率较低(8%)[40-42]；就诊时的其他常见症状包括腹胀、排便习惯改变和疲劳[41]。近期研究发现，直肠出血和缺铁性贫血可使EOCRC发生风险增加10倍[43]。EOCRC最常发生在直肠(35%~37%)，其次是远端结肠(25%~26%)和近端结肠(22%~23%)[44-45]；有29%、27%和29%的LOCRC分别发生在直肠、远端结肠和近端结肠[45]。部分与LOCRC相关的危险因素及其影响大小与解剖部位有一定相关性[46]。例如，与直肠癌相比，体质指数和腰围与结肠癌的关联性更强，而身高和缺乏体力活动的关联却仅限于结肠癌；与结肠癌相比，吸烟与直肠癌的关联性更强[46]。然而，目前尚不清楚EOCRC是否存在这些差异，考虑到早发性直肠癌与早发性结肠癌发病率相比急剧上升，未来应按CRC亚部位进行分层分析[46]。

EOCRC在病理特征方面有一定独特性，肿瘤分化不良和印戒细胞癌比较多见[47]。研究表明，印戒细胞癌(定义为印戒细胞成分超过50%癌细胞)占<30岁的EOCRC的6.1%~6.4%，而30~39岁EOCRC患者人群中这一比例为2.3%~2.4%；40~49岁EOCRC患者人群中占1.0%[34,48]；但LOCRC中印戒细胞癌仅占1.0%~1.6%[34,49]；这提示了EOCRC的潜在分子特征与LOCRC截然不同。

大约30%的EOCRC患者有至少一名一级亲属有CRC家族史[50-52]。一项针对Ⅳ期CRC病例(2 583例)的研究报告发现，与LOCRC相比，EOCRC的*BRAFc.1799T>A*(*p.V600E*)突变较少，微卫星高度不稳定型(microsatellite instability high，MSI-H)肿瘤较多。另一项样本量为18 218例晚期CRC相关的临床研究表明，在非MSI-H肿瘤中，与LOCRC相比，年龄<40岁的EOCRC患者的*APC*突变(66%比80%)和*KRAS*突变(46%比52%)比例均较低；而MSI-H的CRC中，较LOCRC患者，40岁以下EOCRC患者的*BRAF*突变率较低(5.2%比49%)，而*APC*突变率较高(70%比34%)，*KRAS*突变率也较LOCRC高(49%比24%)[53]。此外，EOCRC的另一个公认特征是全基因组低甲基化，这可能与染色体不稳定和不良预后相关[54-55]。进一步研究表明，EOCRC中携带基因突变的发生率为16%，其中一半为Lynch综合征病例[50,52]；另一半包含其他突变，包括腺瘤性结肠息肉病(*APC*突变)、单等位基因和双等位基因*MUTYH*以及*BRCA1/BRCA2*[51]；重要的是，阴性家族史也不能完全排除癌症遗传可能[56]。依赖家族史和肿瘤表型进行遗传胚系检测的临床策略经常会错过致病性变异的携带者，因此，建议所有EOCRC患者均应考虑安排多基因胚系检测[50]。

四、EOCRC的诊治预后情况

由于EOCRC治疗和预后的相关研究证据还很少，故在治疗方面还是与LOCRC基本一致[57]。EOCRC与LOCRC相比预后关联是复杂的。有学者通过分析SEER数据库，发现EOCRC与LOCRC的5年相对生存率分别为67%和61%($P$<0.001)；而Linköping癌症数据库中的这一比例为75%和63%($P$=0.25)[58]。分析原因可能：有远处转移的CRC患者在较年轻的患者中更有可能接受原发肿瘤的手术治疗(调整后比率：72%比63%，$P$<0.001)，而在年轻的CRC患者中接受放射治疗比率也更高(调整后比率：53%比48%，$P$<0.001)[59]。同时，老年患者较年轻患者存在更多合并症，也是导致总体生存率下降的原因之一。然而与中年CRC患者相比，年轻

CRC 患者的死亡风险增加 19%（95%CI：7%~33%），疾病进展风险增加 22%（95%CI：10%~35%）。而年龄效应并不因转移部位、入组年份、接受的治疗类型或生物标志物突变状态有所不同[60]。综上，部分研究认为，EOCRC 患者的生存率较差[60-61]；另一部分研究认为，EOCRC 患者与 LOCRC 生存率相似，甚至更好[58,62-63]。同时，在治疗过程中，EOCRC 患者面对治疗更为积极[59,64-65]。在中国一项单中心回顾性研究中，对 34 067 例 CRC 病例的对比研究发现，从 2000 年到 2021 年，EOCRC 和 LOCRC 病例数均明显增加。与 LOCRC 相比，EOCRC 更具侵袭性，TNM 分期更晚，接受更积极的手术治疗和围手术期治疗比例更高，但两组的无病生存和总生存相似[66]。另外一项基于军事卫生系统数据的研究发现，EOCRC 患者接受术后全身化疗疗程比 LOCRC 患者人数（年龄 65~75 岁）多 2~8 倍[67]。但是，目前对于 EOCRC 积极治疗是否可以提高生存率尚未有一致结论[64,67-68]。EOCRC 特定治疗方案的预后特征、临床管理方案和预测预后生物标志物仍有待进一步研究确定。

## 五、展望与未来

近年来，我们在对 EOCRC 的认识以及降低 EOCRC 发病率和死亡率的干预措施方面，不断取得进展。对临床医生和患者进行有关 EOCRC 潜在危险体征和症状的教育，以及针对 50 岁以下人群进行基于指南的筛查，是可能降低 EOCRC 死亡率的关键重点领域。环境因素和 EOCRC 风险的结论大多来自横断面队列研究，只能体现相关性，而不能推断因果关系。为更好地了解潜在机制并确定环境因素与 EOCRC 之间的关系，我们呼吁进行长期前瞻性队列研究。我们还必须借此确定 EOCRC 的驱动因素和预测特征，为包括精准筛查在内的二级预防提供新依据，以改善 EOCRC 治疗疗效提供诊疗新思路。

**利益冲突**　所有作者声明无利益冲突

## 参 考 文 献


[1] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. CA Cancer J Clin, 2018, 68(6): 394-424. DOI: 10.3322/caac.21492.

[2] Han B, Zheng R, Zeng H, et al. Cancer incidence and mortality in China, 2022[J]. J Natl Cancer Cent, 2024,4(1): 47-53. DOI:10.1016/j.jncc.2024.01.006.

[3] Patel SG, Ahnen DJ. Colorectal cancer in the young[J]. Curr Gastroenterol Rep, 2018,20(4):15. DOI:10.1007/s11894-018-0618-9.

[4] Mauri G, Sartore-Bianchi A, Russo AG, et al. Early-onset colorectal cancer in young individuals[J]. Mol Oncol, 2019, 13(2):109-131. DOI:10.1002/1878-0261.12417.

[5] Bailey CE, Hu CY, You YN, et al. Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975-2010[J]. JAMA Surg, 2015,150(1): 17-22. DOI:10.1001/jamasurg.2014.1756.

[6] Murphy CC, Singal AG, Baron JA, et al. Decrease in incidence of young-onset colorectal cancer before recent increase[J]. Gastroenterology, 2018, 155(6): 1716-1719. DOI:10.1053/j.gastro.2018.07.045.

[7] Siegel RL, Torre LA, Soerjomataram I, et al. Global patterns and trends in colorectal cancer incidence in young adults[J]. Gut, 2019, 68(12): 2179-2185. DOI: 10.1136/gutjnl-2019-319511.

[8] Vuik FE, Nieuwenburg SA, Bardou M, et al. Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years[J]. Gut, 2019, 68(10): 1820-1826. DOI: 10.1136/gutjnl-2018-317592.

[9] Zhao J, Xu L, Sun J, et al. Global trends in incidence, death, burden and risk factors of early-onset cancer from 1990 to 2019[J]. BMJ Oncology, 2023,2(1):e000049.

[10] Stoffel EM, Murphy CC. Epidemiology and mechanisms of the increasing incidence of colon and rectal cancers in young adults[J]. Gastroenterology, 2020,158(2): 341-353. DOI:10.1053/j.gastro.2019.07.055.

[11] Lui RN, Tsoi K, Ho J, et al. Global increasing incidence of young-onset colorectal cancer across 5 continents: a joinpoint regression analysis of 1, 922, 167 cases[J]. Cancer Epidemiol Biomarkers Prev, 2019, 28(8): 1275-1282. DOI: 10.1158/1055-9965.EPI-18-1111.

[12] Siegel RL, Fedewa SA, Anderson WF, et al. Colorectal cancer incidence patterns in the United States, 1974-2013 [J]. J Natl Cancer Inst, 2017, 109(8): djw322. DOI: 10.1093/jnci/djw322.

[13] Low EE, Demb J, Liu L, et al. Risk factors for early-onset colorectal cancer[J]. Gastroenterology, 2020, 159(2): 492-501. DOI: 10.1053/j.gastro.2020.01.004.

[14] Gausman V, Dornblaser D, Anand S, et al. Risk factors associated with early-onset colorectal cancer [J]. Clin Gastroenterol Hepatol, 2020 ,18(12):2752-2759.DOI: 10.1016/j.cgh.2019.10.009

[15] Rosato V, Bosetti C, Levi F, et al. Risk factors for young-onset colorectal cancer[J]. Cancer Causes Control, 2013, 24(2):335-341. DOI: 10.1007/s10552-012-0119-3.

[16] Nguyen LH, Liu PH, Zheng X, et al. Sedentary behaviors, TV viewing time, and risk of young-onset colorectal cancer[J]. JNCI Cancer Spectr, 2018,2(4):pky073. DOI:10.1093/jncics/pky073.

[17] Liu PH, Wu K, Ng K. Association of obesity with risk of early-onset colorectal cancer among women [J]. JAMA Oncol, 2019, 5(1): 37-44. DOI: 10.1001/jamaoncol. 2018.4280.

[18] Sung H, Siegel RL, Rosenberg PS, et al. Emerging cancer trends among young adults in the USA: analysis of a population-based cancer registry[J]. Lancet Public Health, 2019, 4(3): e137-e147. DOI: 10.1016/S2468-2667(18)30267-6.

[19] Chen H, Zheng X, Zong X, et al. Metabolic syndrome, metabolic comorbid conditions and risk of early-onset colorectal cancer[J]. Gut, 2021,70(6):1147-1154. DOI: 10.1136/gutjnl-2020-321661.

[20] Zheng X, Hur J, Nguyen LH, et al. Comprehensive assessment of diet quality and risk of precursors of early-onset colorectal cancer[J]. J Natl Cancer Inst, 2021, 113(5):543-552. DOI: 10.1093/jnci/djaa164.

[21] Rex DK, Boland CR, Dominitz JA, et al. Colorectal cancer screening: recommendations for physicians and patients from the U.S. multi-society task force on colorectal cancer [J]. Am J Gastroenterol, 2017,112(7):1016-1030. DOI: 10.1038/ajg.2017.174.

[22] Wolf A, Fontham E, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society[J]. CA Cancer J Clin, 2018,68(4):250-281. DOI: 10.3322/caac.21457.

[23] Fedewa SA, Siegel RL, Goding Sauer A, et al. Colorectal cancer screening patterns after the American Cancer Society's recommendation to initiate screening at age 45 years[J]. Cancer, 2020, 126(6): 1351-1353. DOI: 10.1002/cncr.32662.

[24] Peterse E, Meester R, Siegel RL, et al. The impact of the rising colorectal cancer incidence in young adults on the optimal age to start screening: microsimulation analysis I to inform the American Cancer Society colorectal cancer screening guideline[J]. Cancer, 2018,124(14):2964-2973. DOI:10.1002/cncr.31543.

[25] Abualkhair WH, Zhou M, Ahnen D, et al. Trends in incidence of early-onset colorectal cancer in the United States among those approaching screening age[J]. JAMA Netw Open, 2020,3(1):e1920407. DOI: 10.1001/jamanetworkopen.2019.20407.

[26] Ladabaum U, Dominitz JA, Kahi C, et al. Strategies for colorectal cancer screening[J]. Gastroenterology, 2020, 158(2):418-432. DOI:10.1053/j.gastro.2019.06.043.

[27] 朱柠, 黄彦钦, 宋永茂, 等. 高危因素量化问卷与亚太结直肠癌筛查评分及分别联合粪便免疫化学检测在进展期结直肠肿瘤筛查中效果的比较[J]. 中华胃肠外科杂志, 2022, 25(7):612-620. DOI:10.3760/cma.j.cn441530-20211127-00478.

[28] Zhu Y, Li X, Hu Y, et al. Nonadherence to referral colonoscopy after positive fecal immunochemical test results increases the risk of distal colorectal cancer mortality[J]. Gastroenterology, 2023, 165(6): 1558-1560.e4. DOI:10.1053/j.gastro.2023.08.013.

[29] Enwerem N, Cho MY, Demb J, et al. Systematic review of prevalence, risk factors, and risk for metachronous advanced neoplasia in patients with young-onset colorectal adenoma[J]. Clin Gastroenterol Hepatol, 2021, 19(4):680-689.e12. DOI: 10.1016/j.cgh.2020.04.092.

[30] Lynch KL, Ahnen DJ, Byers T, et al. First-degree relatives of patients with advanced colorectal adenomas have an increased prevalence of colorectal cancer[J]. Clin Gastroenterol Hepatol, 2003,1(2): 96-102. DOI: 10.1053/cgh.2003.50018.

[31] Lieberman DA, Prindiville S, Weiss DG, et al. Risk factors for advanced colonic neoplasia and hyperplastic polyps in asymptomatic individuals[J]. JAMA, 2003, 290(22): 2959-2967. DOI: 10.1001/jama.290.22.2959.

[32] Tsai MH, Xirasagar S, Li YJ, et al. Colonoscopy screening among US adults aged 40 or older with a family history of colorectal cancer[J]. Prev Chronic Dis, 2015,12:E80. DOI: 10.5888/pcd12.140533.

[33] Hogan NM, Hanley M, Hogan AM, et al. Awareness and uptake of family screening in patients diagnosed with colorectal cancer at a young age[J]. Gastroenterol Res Pract, 2015,2015:194931. DOI: 10.1155/2015/194931.

[34] Willauer AN, Liu Y, Pereira A, et al. Clinical and molecular characterization of early-onset colorectal cancer[J]. Cancer, 2019, 125(12): 2002-2010. DOI: 10.1002/cncr.31994.

[35] Kneuertz PJ, Chang GJ, Hu CY, et al. Overtreatment of young adults with colon cancer: more intense treatments with unmatched survival gains[J]. JAMA Surg, 2015, 150(5):402-409. DOI: 10.1001/jamasurg.2014.3572.

[36] Myers EA, Feingold DL, Forde KA, et al. Colorectal cancer in patients under 50 years of age: a retrospective analysis of two institutions' experience[J]. World J Gastroenterol, 2013,19(34):5651-5657. DOI: 10.3748/wjg.v19.i34.5651.

[37] Chen FW, Sundaram V, Chew TA, et al. Advanced-stage colorectal cancer in persons younger than 50 years not associated with longer duration of symptoms or time to diagnosis[J]. Clin Gastroenterol Hepatol, 2017,15(5):728-737.e3. DOI: 10.1016/j.cgh.2016.10.038.

[38] Deng SX, An W, Gao J, et al. Factors influencing diagnosis of colorectal cancer: a hospital-based survey in China[J]. J Dig Dis, 2012, 13(10): 517-524. DOI: 10.1111/j.1751-2980.2012.00626.x.

[39] Ben-Ishay O, Brauner E, Peled Z, et al. Diagnosis of colon cancer differs in younger versus older patients despite similar complaints[J]. Isr Med Assoc J, 2013, 15(6): 284-287.

[40] Kaunitz JD, Ganz T. AGA Clinical practice guidelines on the gastrointestinal evaluation of iron deficiency anemia [J]. Gastroenterology, 2021, 161(1): 362-365. DOI: 10.1053/j.gastro.2021.03.001.

[41] Vajravelu RK, Mehta SJ, Lewis JD, et al. Understanding characteristics of who undergoes testing is crucial for the development of diagnostic strategies to identify individuals at risk for early-age onset colorectal cancer[J]. Gastroenterology, 2021,160(4): 993-998. DOI: 10.1053/j.gastro.2020.11.058.

[42] Frostberg E, Rahr HB. Clinical characteristics and a rising incidence of early-onset colorectal cancer in a nationwide cohort of 521 patients aged 18-40 years[J]. Cancer Epidemiol, 2020,66:101704. DOI: 10.1016/j.canep.2020.101704.

[43] Demb J, Liu L, Murphy CC, et al. Young-onset colorectal cancer risk among individuals with iron-deficiency anaemia and haematochezia[J]. Gut, 2020, 70(8): 1529-1537. DOI: 10.1136/gutjnl-2020-321849.

[44] Siegel RL, Wagle NS, Cercek A, et al. Colorectal cancer statistics, 2023 [J]. CA Cancer J Clin, 2023,73(3):233-254. DOI: 10.3322/caac.21772.

[45] Archambault AN, Su YR, Jeon J, et al. Cumulative burden of colorectal cancer-associated genetic variants is more strongly associated with early-onset vs late-onset cancer [J]. Gastroenterology, 2020, 158(5): 1274-1286. DOI: 10.1053/j.gastro.2019.12.012.

[46] Wang L, Lo CH, He X, et al. Risk factor profiles differ for cancers of different regions of the colorectum [J].

Gastroenterology, 2020, 159(1): 241-256. DOI: 10.1053/j.gastro.2020.03.054.

[47] Yeo H, Betel D, Abelson JS, et al. Early-onset colorectal cancer is distinct from traditional colorectal cancer[J]. Clin Colorectal Cancer, 2017, 16(4): 293-299. DOI: 10.1016/j.clcc.2017.06.002.

[48] Holowatyj AN, Lewis MA, Pannier ST, et al. Clinicopathologic and racial/ethnic differences of colorectal cancer among adolescents and young adults[J]. Clin Transl Gastroenterol, 2019,10(7):e00059. DOI: 10.14309/ctg.0000000000000059.

[49] Inamura K, Yamauchi M, Nishihara R, et al. Prognostic significance and molecular features of signet-ring cell and mucinous components in colorectal carcinoma[J]. Ann Surg Oncol,2015,22(4):1226-1235. DOI:10.1245/s10434-014-4159-7.

[50] Stoffel EM, Koeppe E, Everett J, et al. Germline genetic features of young individuals with colorectal cancer [J]. Gastroenterology, 2018, 154(4): 897-905. DOI: 10.1053/j.gastro.2017.11.004.

[51] Pearlman R, Frankel WL, Swanson B, et al. Prevalence and spectrum of germline cancer susceptibility gene mutations among patients with early-onset colorectal cancer[J]. JAMA Oncol, 2017,3(4):464-471. DOI: 10.1001/jamaoncol.2016.5194.

[52] Mork ME, You YN, Ying J, et al. High prevalence of hereditary cancer syndromes in adolescents and young adults with colorectal cancer [J]. J Clin Oncol, 2015, 33(31):3544-3549. DOI: 10.1200/JCO.2015.61.4503.

[53] Lieu CH, Golemis EA, Serebriiskii IG, et al. Comprehensive genomic landscapes in early and later onset colorectal cancer[J]. Clin Cancer Res, 2019, 25(19): 5852-5858. DOI: 10.1158/1078-0432.CCR-19-0899.

[54] Strum WB, Boland CR. Clinical and genetic characteristics of colorectal cancer in persons under 50 years of age: a review[J]. Dig Dis Sci, 2019, 64(11): 3059-3065. DOI: 10.1007/s10620-019-05644-0.

[55] Antelo M, Balaguer F, Shia J, et al. A high degree of LINE-1 hypomethylation is a unique feature of early-onset colorectal cancer[J]. PLoS One, 2012, 7(9): e45357. DOI: 10.1371/journal.pone.0045357.

[56] Stigliano V, Sanchez-Mete L, Martayan A, et al. Early-onset colorectal cancer: a sporadic or inherited disease? [J]. World J Gastroenterol, 2014, 20(35): 12420-12430. DOI: 10.3748/wjg.v20.i35.12420.

[57] Cavestro GM, Mannucci A, Balaguer F, et al. Delphi initiative for early-onset colorectal cancer (DIRECt) International Management Guidelines [J]. Clin Gastroenterol Hepatol, 2023, 21(3): 581-603. DOI: 10.1016/j.cgh.2022.12.006.

[58] Wang MJ, Ping J, Li Y, et al. The prognostic factors and multiple biomarkers in young patients with colorectal cancer[J]. Sci Rep, 2015,5:10645. DOI: 10.1038/srep10645.

[59] Abdelsattar ZM, Wong SL, Regenbogen SE, et al. Colorectal cancer outcomes and treatment patterns in patients too young for average-risk screening[J]. Cancer, 2016,122(6): 929-934. DOI: 10.1002/cncr.29716.

[60] Lieu CH, Renfro LA, de Gramont A, et al. Association of age with survival in patients with metastatic colorectal cancer: analysis from the ARCAD Clinical Trials Program [J]. J Clin Oncol, 2014, 32(27): 2975-2984. DOI: 10.1200/JCO.2013.54.9329.

[61] Chou CL, Tseng CJ, Shiue YL. The impact of young age on the prognosis for colorectal cancer: a population-based study in Taiwan[J]. Jpn J Clin Oncol, 2017, 47(11): 1010-1018. DOI: 10.1093/jjco/hyx110.

[62] Blanke CD, Bot BM, Thomas DM, et al. Impact of young age on treatment efficacy and safety in advanced colorectal cancer: a pooled analysis of patients from nine first-line phase III chemotherapy trials[J]. J Clin Oncol, 2011,29(20): 2781-2786. DOI: 10.1200/JCO.2010.33.5281.

[63] Schellerer VS, Merkel S, Schumann SC, et al. Despite aggressive histopathology survival is not impaired in young patients with colorectal cancer [J]. Int J Colorectal Dis, 2012,27(1):71-79. DOI: 10.1007/s00384-011-1291-8.

[64] Kolarich A, George TJ, Hughes SJ, et al. Rectal cancer patients younger than 50 years lack a survival benefit from NCCN Guideline-directed treatment for stage II and III disease [J]. Cancer, 2018, 124(17): 3510-3519. DOI: 10.1002/cncr.31527.

[65] Hubbard J, Thomas DM, Yothers G, et al. Benefits and adverse events in younger versus older patients receiving adjuvant chemotherapy for colon cancer: findings from the Adjuvant Colon Cancer Endpoints data set[J]. J Clin Oncol, 2012, 30(19): 2334-2339. DOI: 10.1200/JCO.2011.41.1975.

[66] Gao XH, Li J, Liu LJ, et al. Trends, clinicopathological features, surgical treatment patterns and prognoses of early-onset versus late-onset colorectal cancer: a retrospective cohort study on 34067 patients managed from 2000 to 2021 in a Chinese tertiary center[J]. Int J Surg, 2022,104:106780. DOI: 10.1016/j.ijsu.2022.106780.

[67] Manjelievskaia J, Brown d, Mcglynn KA, et al. Chemotherapy use and survival among young and middle-aged patients with colon cancer [J]. JAMA Surg, 2017, 152(5): 452-459. DOI: 10.1001/jamasurg.2016.5050.

[68] Orsini RG, Verhoeven RH, Lemmens VE, et al. Comparable survival for young rectal cancer patients, despite unfavourable morphology and more advanced-stage disease [J]. Eur J Cancer, 2015,51(13):1675-1682. DOI: 10.1016/j.ejca.2015.06.005.