

综述

结直肠癌和结直肠腺瘤筛查方式的研究进展

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[摘要] 近年来我国结直肠癌 (colorectal cancer, CRC) 发病率和死亡率呈上升趋势, 严重威胁我国居民的生命健康, 并造成了巨大的社会负担。筛查发现早期结直肠癌或腺瘤 (癌前病变) 可有效降低 CRC 发病率和死亡率。因此, 在 CRC 的防治中, 筛查的作用和意义重大。CRC 和结直肠腺瘤的筛查技术包括以下 4 种类型。① 基于粪便的检查: 粪便隐血试验 (fecal occult based test, FOBT)、粪便 DNA 检测、粪便菌群标志物检测和粪便 M2 型丙酮酸激酶 (M2 pyruvate kinase, M2-PK) 检测。② 影像学检查: 计算机断层结肠成像 (computed tomographic colonography, CTC)、双对比钡灌肠 (double-contrast barium enema, DCBE) 和结肠胶囊内镜检查 (colon capsule endoscopy, CCE)。③ 内窥镜检查: 柔性乙状结肠镜 (flexible sigmoidoscopy, FS) 和结肠镜 (colonoscopy, CS)。④ 液体活检: 循环肿瘤细胞、循环肿瘤 DNA (circulating tumor DNA, ctDNA)、循环肿瘤 RNA (circulating tumor RNAs, ctRNAs)、蛋白质标志物、细胞外囊泡 (extracellular vesicles, EVs) 等。其中生物标志物 DNA 和 RNA 分子等可传达出丰富的人体健康状态信息, 在筛查 CRC 中具有高敏感度和特异度, 但在筛查腺瘤方面尚未广泛开展, 需要对相关生物标志物开展更深入大规模的随机研究。该文对 CRC 和结直肠腺瘤筛查技术进行综述, 介绍其原理、特点以及最新的研究进展, 为 CRC 和结直肠腺瘤筛查技术在临床上的应用提供理论依据。

[关键词] 结直肠癌; 结直肠腺瘤; 筛查**[DOI]** 10.3969/j.issn.1674-8115.2022.05.017 **[中图分类号]** R735.3 **[文献标志码]** A

Research advances in screening modalities for colorectal cancer and colorectal adenoma

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[Abstract] In recent years, the incidence and mortality of colorectal cancer (CRC) in China are on the rise, which seriously threatens the life and health of Chinese residents and causes a huge social burden. Screening to detect early colorectal cancer or adenoma (precancerous lesions) can effectively reduce the incidence and mortality of CRC. Therefore, the role and significance of screening in the prevention and treatment of CRC is significant. There are 4 types of screening techniques for CRC and colorectal adenoma. ① Stool-based tests: fecal occult based test (FOBT), fecal DNA test, fecal flora marker test, and fecal M2 pyruvate kinase (M2-PK) test. ② Imaging tests: computed tomographic colonography (CTC), double-contrast barium enema (DCBE), and colon capsule endoscopy (CCE). ③ Endoscopy: flexible sigmoidoscopy (FS) and colonoscopy (CS). ④ Liquid biopsies: circulating tumor cells, circulating tumor DNA (ctDNA), circulating tumor RNAs (ctRNAs), protein markers, extracellular vesicles (EVs), etc. Among them, biomarkers DNA and RNA molecules can convey rich information about human health status and have high sensitivity and specificity in screening CRC, but they have not been widely carried out in screening adenomas, and more in-depth large-scale randomized studies of relevant biomarkers are needed. The review of CRC and colorectal adenoma screening technologies is present, introducing their principles, characteristics, and recent research advances to provide a theoretical basis for the clinical application of CRC and colorectal adenoma screening technologies.

[Key words] colorectal cancer; colorectal adenoma; screening

结直肠癌 (colorectal cancer, CRC) 是世界上最常见的恶性肿瘤之一, 发病率和死亡率分别高达 10.0% 和 9.4%, 位居世界第三位和第二位^[1]。近年

来, 随着我国生活方式和饮食结构的改变, CRC 分别位居全国恶性肿瘤发病率和死亡率的第二位和第五位^[2], 给我国 CRC 的预防、诊断、治疗带来了巨

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大的挑战。腺瘤-癌途径是CRC发生的主要途径,是指从正常肠道黏膜改变发展为腺瘤、早期癌,最终发展为转移性癌症^[3]。研究表明,筛查出的早期CRC患者在经过治疗后,其5年生存率高达90%以上^[4],而晚期CRC患者的5年生存率仅为12%^[5]。我国85%以上的CRC发现即已属晚期,即使经过手术、放射治疗(放疗)、化学治疗(化疗)和靶向治疗,生存率仍明显低于40%^[6]。因此为了更好地防治CRC,开展全民CRC和腺瘤的早期筛查迫在眉睫。筛查计划的目的是在可治愈的阶段或仍处于非恶性前兆阶段(结直肠腺瘤)时发现和切除病变,从而有效降低CRC的死亡率^[7-8]。

目前CRC和结直肠腺瘤的筛查技术包括基于粪便的检查、影像学检查、内窥镜检查 and 液体活检等。

1 基于粪便的检查

基于粪便的检查包括粪便隐血试验(fecal occult based test, FOBT)、粪便DNA检测、粪便菌群标志物检测、粪便M2型丙酮酸激酶(M2 pruvate kinase, M2-PK)检测等。

1.1 FOBT

较大的息肉或CRC由于局部血供丰富,易在排便过程中破裂出血,表现为大便与血液混合,如果出血量较少(消化道出血在5~50 mL)则表现为隐匿性消化道出血。目前临床检测隐匿性消化道出血最常用的方法是FOBT。FOBT是CRC无创筛查重要的手段之一,包括愈创木脂化学法(guaiac-based FOBT, gFOBT)和免疫化学法(fecal immunochemical test, FIT)。gFOBT通过过氧化物酶活性检测血红蛋白(Hb)的亚铁离子,其检测结果易受饮食和药物影响,可能出现假阴性结果,遗漏小息肉或不出血的息肉^[9-10],因此特异性不强。FIT是利用特定的抗体进行的一种免疫化学试验,在检测CRC方面更加敏感和准确(灵敏度69%~95%)^[11-13],而且不需要饮食限制,已经取代了gFOBT。因此大多数人群筛查项目使用FIT作为结肠镜检查(colonoscopy, CS)的分流测试^[14]。在这种情况下,所有FIT阳性的参与者都会被建议转诊CS,以发现和切除腺瘤和早期癌症。目前,市售的FIT产品主要有2种形式:定性FIT产品和定量FIT产品。研究分析表明,使用自动粪便血液分析仪

(OC-SENSOR, Eiken Chemical Co. Ltd, 日本)进行的定量测试比使用免疫金标记FIT试纸(HemoSure, WHPM Co. Ltd, 北京)的定性测试有更多优势,定量试验提高了CRC和结直肠腺瘤的阳性预测值^[15]。因此,大型国家项目和临床试验经常使用定量测试。但是FIT对晚期结直肠腺瘤的敏感性较低,其中10 µg Hb/g 阈值时的敏感度为40%,特异度为95%^[16]。因此,提高无创、便捷和价廉的粪便检测的敏感性是CRC筛查更具成本效益和效率的方法^[17-19]。

1.2 粪便DNA检测

粪便DNA检测是运用分子生物学方法检测粪便样本中脱落的肿瘤细胞中的变异DNA,从而判断个体是否患有结直肠腺瘤或CRC。粪便DNA检测包括单靶点和多靶点方案,也可与FIT联合使用。它具有无创、无需限制饮食、无需特殊设备等优点^[20]。多靶点检测工具DNA ColoGuard (Multitarget stool DNA test, MT-sDNA; Exact Sciences Corporation, 美国)是一种替代性粪便测试,将粪便DNA标记(包括KRAS基因突变、NDRG4和BMP3基因甲基化异常和β-肌动蛋白的定量分子检测)与FIT的结果相结合,在近10 000人群样本中进行测试,结果显示:与FIT相比,MT-sDNA在预测CRC和晚期腺瘤方面有较高的敏感度(分别为92.3% vs 73.8%; 42.2% vs 23.8%),并保持了较高的特异度(89.9% vs 96.4%)^[21]。我国进行了一项病例对照研究^[22]显示:使用FIT-DNA检测试剂盒ColoClear (New Horizon Health Technology Co. Ltd, 杭州),将FIT检测与KRAS基因突变、NDRG4和BMP3甲基化异常的检测相结合,FIT-DNA试剂盒在预测晚期腺瘤方面可能比FIT具有更好的敏感度(53.1% vs 36.7%),但是在预测CRC方面没有明显差异。然而,尽管做出了这些努力来改进基于粪便的筛查,但其主要的缺点仍然是费用昂贵,成本效益低,很难广泛应用于CRC筛查^[23]。

1.3 粪便菌群标志物检测

粪便菌群标志物应用于临床检测CRC和晚期腺瘤的研究受到了越来越多的关注。标记具核梭形杆菌(*Fusobacterium nucleatum*, Fn)可以提高FIT诊断性能,为单独检测FIT可能遗漏的病变提供了查漏价值。标记Fn与FIT联合检测时,检出CRC和腺瘤的敏感度比单独的FIT有显著提高(分别为92.3% vs 73.1%;

38.6% vs 15.5%)^[24]。一项研究^[25]显示: CRC组粪便Fn和pks+大肠杆菌的含量明显高于结直肠腺瘤组和健康对照组,但是在肿瘤分布部位以及区分CRC和结直肠腺瘤方面无明显差异。粪便菌群标志物的主要缺点在于分析方法复杂,所需价格昂贵,用于CRC筛查的确切价值还需大样本人群筛查研究进一步明确。

1.4 粪便M2-PK检测

肿瘤细胞中的M2-PK主要以二聚体形式存在,可以促进肿瘤的增殖和转移。在CRC和腺瘤患者中,它可以从肿瘤细胞释放到血液中,也可以释放到患者的粪便中。研究^[26]表明: CRC和结直肠腺瘤患者粪便中M2-PK的水平显著高于健康人群,在CRC和腺瘤的敏感度分别为92.8%和69.4%,均明显高于FOBT,但是在特异性方面无明显差异。粪便M2-PK检测的优势在于其成本实惠、使用方便和结果快速,但是目前尚需进一步研究认证其筛查效果。

2 影像学检查

影像学检查包括计算机断层结肠成像(computed tomographic colonography, CTC)、双对比钡灌肠(double-contrast barium enema, DCBE)和结肠胶囊内镜检查(colon capsule endoscopy, CCE)。

2.1 CTC

CTC通过重建计算机断层扫描或磁共振的空气悬浮结肠图像,提供结肠的二维和三维管腔内图像。欧洲胃肠镜学会指南建议把CTC作为诊断CRC的首选放射学检查^[27]。但CTC的总体敏感度和特异度分别为66.8%和80.3%,均低于CS。而对于>10 mm的息肉,CTC显示出91.2%的敏感度和87.3%的特异度^[28]。由于CTC为无创检查,发生肠穿孔的风险非常低,也不需要镇静^[29],因而患者更易接受。但CTC阳性结果后仍需要后续的CS,继而对病变进行切除或活检。且CTC需要患者进行积极的肠道准备,使患者暴露于辐射,并且缺乏标准化方法导致诊断性能参差不齐。

2.2 DCBE

日本一项研究发现,DCBE在CRC和结直肠腺瘤中的特异性明显低于CS,但DCBE的敏感性高于

CS,且可以作为诊断大规模黏膜下浸润性CRC的辅助手段^[30]。DCBE在过去被认为是一种安全的方法经常使用,但与CTC的缺点相似,需要在阳性结果后进行后续CS。随着CS的出现,它的使用已大大减少^[31]。现阶段钡餐研究在筛查CRC方面主要由内窥镜或CTC取代,其使用持续减少可能会进一步对其性能质量产生负面影响,目前临床多用于评估非肿瘤性疾病,如炎症性肠病(inflammatory bowel disease, IBD)^[32]。

2.3 CCE

在非肿瘤性梗阻的患者中,CCE可以被认为是CTC的替代方案,用以探索近端结肠段病变的情况^[27]。文献报道93%的病例中,第二代CCE可以补充不完整的CS,并有助于检测其他相关的结肠和结肠外病变^[33]。SPADA等^[34]在一项前瞻性、单盲、头对头的研究中,比较了CTC和CCE在未完成CS患者中的作用;在这项研究中,CCE在24.5%的患者中识别了≥6 mm的息肉[95%置信区间(confidence interval, CI) 16.6%~34.4%],CTC仅在12.2%的患者中识别了息肉(95%CI 6.8%~20.8%),相对敏感度为2.0(95%CI 1.34~2.98),这表明使用CCE时对病变≥6 mm病变的敏感性明显增加。在另一项695例患者的前瞻性多中心研究中,CCE对≥6 mm腺瘤的敏感度和特异度分别为88%和82%,这对于不能接受CS或做过不完全CS的患者来说是足够的^[35],但CCE成本更高,且缺乏切除或活检病变的能力,因此仅能作为CS的替代选择。

3 内窥镜检查

内窥镜检查包括柔性乙状结肠镜(flexible sigmoidoscopy, FS)和CS检查。

3.1 FS

FS只显示远端肠道,不能发现近端结肠的病变。但FS的优点包括不需要饮食限制,而且涉及最少的肠道准备^[36-37]。在一项随机对照试验中,FS可将筛查患者的CRC发生率和死亡率分别降低26%和30%^[38]。但我国38%的结肠腺瘤和42%的CRC位于近端结肠,使用FS可能遗漏大量病变^[39]。

3.2 CS

CS在检测癌症和癌前病变方面具有很高的敏感度和特异度,CS下活检病理是诊断CRC的金标准。在检查过程中,也可以同时切除病变或活检以进行组织学评价^[40-41]。一项大型meta分析表明:与FS相比,CS对整个大肠和小肠远端的癌和癌前病变有很高的敏感度和特异度(97%~98%),CS可降低近端结肠癌的死亡率^[40]。良好的肠道准备和规范的CS操作是降低漏诊率的关键,然而检查过程中的不适感和并发症的发生是部分患者畏惧并拒绝检查的原因。研究^[36,42]表明:有0.1%~0.2%的患者发生出血或肠穿孔等并发症。但鉴于CS的高敏感度与高特异度,并兼具诊断和活检、切除腺瘤和早期CRC的功能,其具备不被取代性^[43]。

4 液体活检

液体活检是一个统称,是指分析癌症患者生物液体中分离出来的肿瘤生物标志物。外周血是液体活检的主要来源,包括循环肿瘤细胞、循环游离DNA(circulating free DNA, cfDNA)或RNA以及含有蛋白质的外泌体、核酸和脂质^[44]。对生物液体中的肿瘤生物标志物进行分析,有可能提高筛查人群的参与率^[45]。外周血是研究最多的生物液体之一,对于无症状的、中等风险的、不愿意接受粪便检查或内窥镜检查的人来说,准确的血液检测可能是一种有吸引力的选择。在一项临床试验中,12%拒绝粪便筛查的患者同意进行外周血的测试^[46]。

4.1 循环肿瘤细胞

循环肿瘤细胞是从外周血中分离出来的肿瘤细胞。研究表明循环肿瘤细胞的计数可以作为肿瘤进展和治疗反应的潜在标志物^[47]。我国一项研究^[48]显示:以CS检查结果为参考,循环肿瘤细胞检测出腺瘤和CRC的敏感度分别为95.2%和79.2%。然而,循环肿瘤细胞的稀有性和异质性以及检测和分析技术的局限性限制了循环肿瘤细胞作为一种新的生物标志物的被广泛接受和应用。

4.2 循环肿瘤DNA

cfDNA存在于外周血、尿液、腹水和胸水中,主要来自血液系统、胃肠道和皮肤的凋亡细胞。具有

肿瘤特异性突变的cfDNA被称为循环肿瘤DNA(circulating tumor DNA, ctDNA)。ctDNA片段主要来源于凋亡或坏死的肿瘤细胞^[49]。对经常与肿瘤发生有关的基因中的cfDNA突变进行评估,发现ctDNA是一种很有前途的预测CRC的生物标志物,可以帮助识别CRC的早期病变及监测肿瘤复发^[50]。ctDNA检测作为肿瘤转移与原发肿瘤之间的纽带,可实时反映肿瘤进展情况,对肿瘤分期具有参考价值。研究^[51-52]发现: CRC患者的ctDNA的平均浓度远远高于健康人群, CRC早期患者的ctDNA浓度明显低于晚期患者,并且ctDNA浓度与肿瘤大小呈正相关。ctDNA的水平可以表明其预后价值。最近的研究发现,监测CRC患者的ctDNA水平可以比传统的肿瘤标志物或放射诊断更早显示疾病复发和对治疗的反应^[53]。ctDNA以其易于获取和克服肿瘤空间异质性的特点,可用于垂直检测肿瘤患者的突变状态,并根据患者肿瘤的分子特征进行个体化治疗。BETTEGOWDA等^[54]利用外周血ctDNA检测206例CRC患者的KRAS基因突变,发现敏感度达到87.2%,特异度高达99.2%。近期我国一项前瞻性队列研究显示,单个ctDNA甲基化标志物(cg10673833)在检测1493例高风险人群的CRC和癌前病变时有89.7%的灵敏度和86.8%的特异度^[55]。Septin9(SEPT9)是血液中与CRC有关的最广泛研究的DNA标志物之一。在无症状人群的筛查中,检测循环中甲基化SEPT9(methylation SEPT9, mSEPT9)的EpiProcolon检测法的敏感度从61.2%到82.2%不等,特异度从83.6%到95.1%不等,比癌胚抗原(carcinoembryonic antigen, CEA)和FIT测试表现更好^[56-59]。然而, mSEPT9不能区分CRC、息肉或腺瘤,而且不受肿瘤定位的影响,但可能受年龄或性别的影响,这表明需要有特定年龄和性别的界限,以更好地优化筛查和诊断程序。由此可见,需要进一步的临床研究来验证ctDNA是否能成为无创筛查CRC和结直肠腺瘤的标志物。

4.3 循环肿瘤RNA

循环肿瘤RNA(circulating tumor RNAs, ctRNAs)包括微小RNA(micro RNA, miRNA)、其他非编码RNA(non-coding RNA, ncRNA)和信使RNA(messenger RNA, mRNA)。miRNA是过去10年中研究最多的一种类型,可能是CRC中描述最广

泛的非侵入性生物标志物。它们在血清和粪便样本中都能检测到,可以以2种形式释放到血液中,要么与RNA结合蛋白联合,要么包装在外泌体中,两者都为体液中的RNA提供保护和稳定性^[60]。有证据表明,一些miRNAs的水平在CRC中会发生改变,并且miRNAs会调节促进癌症的RAS基因^[61]。我国进行了一项纳入35项研究的meta分析,共涉及3 258例CRC患者和2 683例健康人,发现miRNA在检测CRC方面有很好的表现,敏感度为80% (95%CI 0.75~0.83),特异度为80% (95%CI 0.75~0.84)^[62]。YAN等^[63]进行的一项包含103项研究的meta分析显示,在亚洲人中比较血浆、血液、组织和粪便等样本,从血清样本中获得的miRNAs对检测CRC更有帮助。然而,目前还没有相关的诊断产品可广泛用于临床,这意味着需要进行更多的研究,以便将这些标志物用于临床筛查环境中。

4.4 蛋白质标志物

血液中可能存在CRC标记的蛋白质分子数量很多。然而,目前仅有2种基于血液的主要生物标志物可用于检测CRC患者:CEA和糖类抗原19-9(carbohydrate antigen 19-9, CA19-9)^[64]。但是CEA和CA19-9的浓度在其他疾病或肿瘤中也可能很高。例如CEA在肝脏疾病、胰腺炎、IBD和其他恶性肿瘤可能会引起较高的水平,CA19-9在胰腺和胆道恶性肿瘤中浓度较高,可见它们在CRC早期筛查方面缺乏敏感度和特异度,因此它们作为CRC筛查的生物标志物是否有用仍是一个尚未解决的问题^[65-66]。如今CEA和CA19-9被用于检测转移性疾病、复发或监测对治疗的反应,并在临床实践中得到批准^[67-68]。这些结果表明,在早期检测CRC方面需要有更可靠的新分子。BHARDWAJ等^[69]在2020年进行了一项研究,选取年龄和性别匹配的98例新诊断的CRC患者和100例通过CS筛查的健康对照者,并使用56例CRC患者和102例健康对照者进行外部验证,通过测量他们血浆样本的275个亲蛋白标志物的水平,发现一个12个标志物的算法(包括AREG、CEA、GZMB、ITGAV、KRT19、MCP1、PON3、TR、MASP1、RAR-RES2、S100A4和TRAP)在检测早期CRC方面特别有希望,在验证组中显示61%的敏感度和80%的特异度,曲线下面积(area under the curve, AUC)=0.75 (95%CI 0.67~0.84)。但是它

们可能不适合常规测试,因为在进行检测实验之前,这些测试所需的技术更加复杂,且价格更加昂贵,因此将蛋白质生物标志物作为临床检测早期CRC方法的依据仍不充分。

4.5 细胞外囊泡

细胞外囊泡(extracellular vesicles, EVs)如外泌体(exosomes, EXOs)、微囊泡(microvesicles, MVs)和大囊泡,可能包含有希望的生物标志物。EVs含有蛋白质、RNA、DNA和脂质,部分反映了起源细胞的组成。通过保护核酸不被降解,与无细胞核酸相比,EVs也被认为是肿瘤分子分析的更好的未来标志物^[70]。EVs也可由癌细胞分泌的,而且数量比正常细胞多,它增加了参与癌症进展的RNAs、生长因子和趋化因子的转移^[71]。通过比较CRC患者和健康对照组的血清EV-miRNA,YAN等^[72]发现miR-486明显上调,而miR-548c明显下调。研究EVs和EXOs的重要不足是缺乏从血液中分离出EVs并提取其内容或表面物质的标准化方案,需要后续进一步深入研究。

5 总结与展望

目前,CRC的筛查方法多样,包括最常用的FIT,作为诊断金标准的CS和病理检查,辅助诊断的CTC,以及尚待完善的基于粪便和血液的生物标志物筛查等。作为金标准的CS有创且依赖医师的技术水平,一些无创的新的研究试图在粪便或血液样本中发现癌症生物标志物。然而,大多数已确定的生物标志物(M2-PK、DNA、RNA、EVs等)仅在初步的病例对照研究中进行了评估。为了改善CRC和结直肠腺瘤的筛查和诊断,需要进行大规模的随机对照研究以确认这些生物标志物的临床效益和实用性。

利益冲突声明/Conflict of Interests

作者宣称没有利益冲突。

The authors declare no conflicts of interest.

作者贡献/Authors' Contributions

赵敏、彭海霞参与了论文内容设计;赵敏、褚以恣、彭海霞参与了论文的写作与修改。所有作者均阅读并同意了最终稿件的提交。

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