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文献综述 REVIEW

# 遗传性非息肉性结直肠癌

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## Hereditary nonpolyposis colorectal cancer

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## Abstract

Hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome, is a class of autosomal dominant genetic disease. Main clinical characteristics of HNPCC include early onset age, more common in the right colon, and concomitant with simultaneous or metachronous extracolonic cancers, including endometrial cancer, stomach cancer, and ovarian cancer. However, the prognosis of HNPCC is better than sporadic colorectal cancer. Screening and intervention for HNPCC among high-risk pedigree population can effectively reduce the cancer incidence and mortality. In this article we will review the pathogenesis, epidemiology, diagnosis, screening, prevention and treatment of HNPCC.



Key Words: Hereditary nonpolyposis colorectal cancer; Mismatch repair gene; Microsatellite instability; Diagnosis and screening

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## 摘要

遗传性非息肉性结直肠癌(hereditary nonpolyposis colorectal cancer, HNPCC)又称为lynch综合征(lynch syndrome, LS)是一种常染色体显性遗传性疾病. 临床特点是: 发病年龄早, 多见于右半结肠, 伴同时性或异时性肠外恶性肿瘤如子宫内膜癌、胃癌、卵巢癌等, 预后比散发性结直肠癌好. 对高危家系人群的筛查和干预能有效降低结直肠及肠外恶性肿瘤的发生率和死亡率. 本文对HNPCC发病机制、流行病学、临床诊断、筛查、预防和治疗做一综述.



**关键词: 遗传性非息肉性结直肠癌; 错配修复基因; 微卫星不稳定; 诊断筛查**

**核心提示:** 随着我国家系日益小型化难以收集完整家族史资料, 在临床收治工作中Bethesda指南更适合用于临床初筛. 对于满足Bethesda指南任意一条的患者临床医生都应当引起重视. 对于所有符合临床诊断标准的患者进行IHC/MSI检测将很大程度上提高HNPCC的诊断率.

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## 0 引言

1966年Lynch等报道了两个家族的成员中聚集性高发结直肠癌、胃癌和子宫内膜癌, 并命名为“癌症家族综合症”. Lynch还把本病分为

**■背景资料**
遗传性非息肉性结直肠癌(hereditary non-polyposis colorectal cancer, HNPCC)是一种由于错配修复基因突变导致的常染色体显性遗传性疾病, 外显率约为80%, 约占所有结直肠癌3%左右.

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■研发前沿
如何经济、有效筛查出HNPCC患者是目前国外的研究热点之一.

Lynch Ⅰ型(家族性结直肠癌综合征, 家族呈现结直肠癌遗传)及Lynch Ⅱ型(家族性癌症综合征, 家族呈现结直肠癌和其他肿瘤遗传), 后来统称为HNPCC[1-3]. HNPCC是一种常染色体显性遗传病, 外显率约为80%[4], 约占所有结直肠癌的3%左右[5].

## 1 HNPCC的发病机制及分子生物学特征

目前研究认为DNA错配修复基因(DNA mismatch repair, *MMR*)的突变导致HNPCC[5,6]. 已知与HNPCC发病相关的错配修复基因有以下7种*MLH1*、*MSH2*、*MSH6*、*PMS1*、*PMS2*、*MLH3*、*EXO1*, 其中临床最常见是*MSH2*、*MLH1*、*PMS2*、*MSH6*, 其突变率分别为38%、32%、15%和14%[7,8]. 在HNPCC患者中携带不同的突变基因其患癌风险不尽相同. Engel等[9]报道*MLH1*或*MSH2*突变携带者中其患癌风险高于*MSH6*, *MSH6*突变携带者患癌风险高于PMS2. 同散发性结直肠癌一样, 男性突变携带者罹患结直肠癌风险高于女性.

在部分患者中*MMR*启动子甲基化可能与HNPCC相关[10,11]. Zhou等[12]对18例未发现已知相关*MMR*突变的HNPCC家系先证者进行*MLH1*启动子甲基化检测, 发现5例先证者存在*MLH1*启动子甲基化. Morak等[13]研究发现在HNPCC家系中存在*MLH1*启动子甲基化, 并认为携带*MLH1*启动子甲基化具有可遗传性.

90%以上的HNPCC患者检测到微卫星不稳定(microsatellite instability, MSI)现象[14,15]. 微卫星DNA(microsatellite DNA)是一类短串联重复序列, 在DNA复制过程中容易发生滑动, 致使模板链或新生链可能产生一个小型环状结构. 在错配修复功能正常时很容易被修复, 如果错配修复功能缺陷, 这种“DNA环状结构”将随复制的进行而存在下去, 导致MSI产生[16]. 约12%的散发性结直肠癌中也存在MSI, 但致病机制与HNPCC截然不同. MSI的散发性结直肠癌致病原因多与*MLH1*启动子甲基化相关且存在*BRAF*基因V600E突变[17-22], 但是在HNPCC中尚未发现*BRAF*基因的突变[5]. 另外40%-45%符合Amsterdam诊断标准的患者中并没有发现MSI, 基因检测也没有发现已知的MMR突变. 与HNPCC患者比较这类患者患结直肠癌风险低, 发病年龄较晚, 且没有证据表明肠外肿瘤的风险增高, 被称为“家族性结直肠癌X型”[15,23,24].

## 2 HNPCC的临床病理特征

临床上HNPCC患者结直肠癌发病年龄早, 多在50岁以前(平均发病年龄45岁), 好发于右半结肠, 如仅采取单纯肠切除术25%-30%的患者10年内会发生异时性肠癌. 约30%患者十年之内会患上HNPCC相关的其他肿瘤[24], 但其预后较散发性结直肠癌好[25,26]. HNPCC患者终生患结直肠癌风险男性34%-73%、女性32-59%, 患HNPCC相关肿瘤风险分别为子宫内膜癌39%-50%、卵巢癌7%-8%、胃癌1%-6%、输尿管/肾盂癌2%-8%、胆管癌1%-4%、小肠癌1%-4%、中枢神经系统肿瘤大约2%、胰腺癌大约4%、皮脂腺瘤取决于发生突变的*MMR*基因[27-30]. 病理学上HNPCC患者常表现为低分化粘液腺癌或印戒细胞癌、伴肿瘤周围淋巴细胞浸润、Crohn's样淋巴反应[24].

## 3 HNPCC的临床诊断标准

目前国际通用的诊断标准有Amsterdam Ⅰ标准[31]、Amsterdam Ⅱ标准[32]及Bethesda指南[33]. Amsterdam Ⅰ标准是由HNPCC国际合作组织在1991年制定的, 之后在1999年该组织对该标准做了修改称Amsterdam Ⅱ. 1996年美国国家癌症研究所(National Cancer Institute, USA NCI)提出了Bethesda指南, 并在2004年做了修订和简化[5,34]: (1)结直肠癌发病早于50岁; (2)任何年龄诊断的同时和异时性多原发性结直肠癌及HNPCC相关肿瘤; (3)60岁以下结直肠癌组织学诊断发现有肿瘤浸润淋巴细胞、Crohn's样淋巴细胞增生、黏液癌/印戒细胞癌或髓样癌; (4)至少一个一级亲属发生HNPCC相关肿瘤, 且有一个肿瘤发生于50岁之前; (5)至少2个一级或二级亲属发生HNPCC相关肿瘤. 比较上述两个诊断标准Amsterdam标准诊断特异性高(达到99%)而敏感性较低(28%-45%), Bethesda指南诊断敏感性较高(73%-91%)而特异性稍低(77%-82%)[15]. 由于Amsterdam标准在诊断上过分严格限制家族史, 且随着我国家系日益小型化难以收集完整家族史资料, 在临床收治工作中Bethesda指南更适合用于临床初筛. 对于满足Bethesda指南任意一条的患者, 临床医生都应当引起重视.

## 4 HNPCC的实验室筛查

HNPCC的实验室筛查手段包括有MMR突变检测、MSI检测及免疫组织化学检测. MMR突变

表 1 HNPCC诊断筛查策略

| 序号 | HNPCC诊断筛查策略 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | IHC | | | | MSI | *BRAF*V600E突变检测 | *MLH1*启动子甲基化分析 | MMR基因检测(诊断HNPCC金标准) |
| | MLH1 | MSH2 | MSH6 | PMS2 | | | | |
| 1 | + | + | + | + | MSI-L/MSS | UN | UN | SCRC(对符合临床诊断标准应行突变检测) |
| 2 | + | + | + | + | MSI-H | UN | UN | *MMR*突变检测 |
| 3 | UN | UN | UN | UN | MSI-H | UN | UN | IHC(IHC结果判断同下)或/和*MMR*突变检测 |
| 4 | – | + | + | – | UN | + | UN | SCRC |
| | | | | | UN | – | + | SCRC(对符合临床诊断标准应行突变检测) |
| | | | | | UN | – | – | *MLH1*突变检测 |
| 5 | – | + | + | + | UN | UN | UN | *MLH1*突变检测 |
| 6 | + | + | + | – | UN | UN | UN | *PMS2*基因检测没有发现时进一步行*MLH1*突变检测 |
| 7 | + | – | – | + | UN | UN | UN | *MSH2*突变检测没有发现时进一步行*MSH6*突变检测 |
| 8 | + | – | + | + | UN | UN | UN | *MSH2*突变检测 |
| 9 | + | + | – | + | UN | UN | UN | *MSH6*突变检测没有发现时进一步行*MSH2*突变检测 |

所有新诊断的结直肠癌患者或者按照临床诊断标准对患者进行初筛行IHC/MSI检测. +: 蛋白表达正常或突变阳性或者MLH1启动子甲基化阳性; –: 代表蛋白表达缺失或突变阴性或者*MLH1*启动子甲基化阴性; UN: 未检测或者是与结果不相关; SCRC: 散发性结直肠癌.

■相关报道
Heald等认为对所有新诊断的肠癌患者行IHC/MSI检测来筛查HNPCC是一种经济、可行的方法. 要提高HNPCC的临床收治率还需要外科医生、遗传咨询医生及患者的共同配合.

检测是HNPCC诊断的金标准[35], 但基因检测方法复杂和资金耗费多, 且*MMR*突变不存在突变热点区, 使以基因检测去筛检HNPCC存在很大困难. 目前临床上多应用MSI检测和免疫组织化学的方法来确定是否发生MMR突变.

4.1 *MMR*的基因检测 检测*MMR*突变的方法包括单链多态性分析、变性凝胶电泳、蛋白截短实验、变性高效液相色谱分析、多重连接探针扩增技术及直接测序等. 直接测序法敏感性和特异性最高, 但检测费用昂贵. 国外报道认为多重连接探针扩增技术在检测*MMR*突变中更方便和经济, 而且特异性、敏感性比其他检测方法高[36]. 近年来兴起的高通量测序技术使我们对更为细致的分析*MMR*突变全貌成为可能[35].

4.2 MSI检测 MSI是HNPPC肿瘤发生的重要标志. MSI作为最早应用于实验室筛查HNPCC的分子标记, 其敏感性100%, 特异性在90%以上[37]. 经典检测MSI的方法是由NCI提出的以单碱基重复序列BAT-25和BAT-26, 双碱基序列D2S123、D5S346、D17S250这5个微卫星点作为标志物检测肿瘤. 5个位点中如果出现2个及以上位点有重复序列长度的改变称为高频MSI(for high-frequency MSI, MSI-H), 只有一个位点有长度改变称为低频MSI(for low-frequency MSI, MSI-L), 无任何位点的变化称为微卫星稳定(microsatellite stability, MSS)[15,38].

4.3 免疫组织化学 免疫组织化学(immunohistochemistry, IHC)检测错配修复蛋白MLH1、MSH2、MSH6、PMS2的表达也是一种有效的HNPCC筛查方法应用于临床[4,39]. Shia[40]认为免疫组织化学与MSI检测相比较敏感性相近, 但费用更为低廉, 更适用于临床筛查HNPCC患者. 另外IHC结果有助于鉴别突变的基因.

## 5 临床诊断筛查策略

虽然我们可以通过临床诊断标准和实验室检测手段来发现HNPCC患者, 但要从众多结直肠癌患者中查筛查出HNPCC犹如大海捞针. 在德国只有不到一半*HNPCC*基因突变携带者被确诊[5]. 如何采用高效、经济、易行的筛选策略来提高HNPCC的收治率, 成为临床研究的热点之一[41]. 这些策略不仅要考虑到诊断的敏感度和特异性还需综合考虑经济、伦理学及患者的心理负担等方面的问题[42-44]. 目前国外研究表明对所有新诊断的结直肠癌和子宫内膜癌患者行IHC, MSI分析是一种经济、可行的方式[19,45-47]如表1. 2013年NCCN(National Comprehensive Cancer Network, NCCN)结直肠癌指南第一版对这种广泛的筛查方式进行了推荐[22].

## 6 HNPCC的治疗和预防

目前HNPCC的治疗上, 专家推荐采用结肠次全切除术, 虽然相比于传统节段性结肠切除术其总生存率并无差异, 但次全切除术能有效减少异时性肠癌发生概率和手术风险[48]. 但对于老年患者其术后异时性肠癌发生风险低, 结肠次全切除术可能过于激进, 反而增加手术并发症和死亡率[49]. 临床研究表明对于MSI的Ⅱ、Ⅲ

**■创新盘点**
本文对HNPCC的发病机制、流行病学、临床诊断、防治做简要介绍, 以加强临床医生对其认识从而提高HNPCC的诊断率.

期结直肠癌患者并不能从以5-氟尿嘧啶为基础的辅助化疗中获益, 但在HNPCC患者中是否存在相同情况需要进一步研究[5]. 欧洲肿瘤学会(European Society for Medical Oncology, ESMO)指出HNPCC化疗方案应与散发性结直癌一致[48]. HNPCC的预防治疗措施应同时针对患者及高风险的家系成员. 目前临床上提出的预防措施, 还缺乏足够的研究证据. 如预防性手术(预防性肠切除术、预防性子宫、卵巢切除术)及药物预防(阿司匹林和口服避孕药在肠息肉和子宫内膜/卵巢癌上已经分别显示出了一定的预防作用, 但对于预防HNPCC相关的肠癌和子宫内膜/卵巢癌是否有效还缺少研究证据)[48,50]. 大部分专家认为每1到2年的肠镜随访能降低结直肠癌的风险[5]. 德国HNPCC联盟推荐家系成员, 从25岁或者不迟于家族中最小发病年龄5年开始每年进行: 一般体格检查、腹部超声检查、全结肠镜检查、胃镜检查(35岁开始)、女性患者还应进行妇科体检包含阴道超声检查、子宫内膜活检(35岁开始)[5].

## 7 结论

目前我国HNPCC发病率尚无报道. 但我国人口基数大, 且随着结直肠癌发病率和死亡率逐年增加, 使得HNPCC的诊断、防治工作显得更加艰巨. 然而在临床工作中具有遗传背景的HNPCC患者容易被漏诊, 从而导致其高危家系成员丧失早期诊断和治疗的机会. 在我国HNPCC的总体收治率不高的原因有以下几方面: (1)由于临床医生对HNPCC认识不足, 仅有少数医疗单位在开展系统的收治和研究工作; (2)MMR蛋白免疫组织化学检测并未纳入结直肠癌术后常规检测项目; (3)HNPCC的诊断和筛查并未纳入医疗保险服务, 由于经济限制患者难以接受昂贵的基因检测费用; (4)国内缺乏针对此类患者的遗传咨询服务. 但随着我国经济发展, 医学基础和临床研究逐渐与国际接轨, 越来越多的临床医生开始认识和重视HNPCC, 随着对HNPCC临床特点, 遗传特征的深入研究以及基因诊断技术的不断进步, 必然会推动HNPCC的预防、筛查和规范化治疗.

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**■应用要点**

随着对HNPCC临床特点, 遗传特征的深入研究以及基因诊断技术的不断进步, 必然会推动HNPCC的预防、筛查和规范化治疗.

**■同行评价**
本文对HNPCC的发病机制、流行病学、临床诊断及防治做了简要介绍, 对本病的临床诊治起到了一定的提示作用, 具有一定的临床应用价值.


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