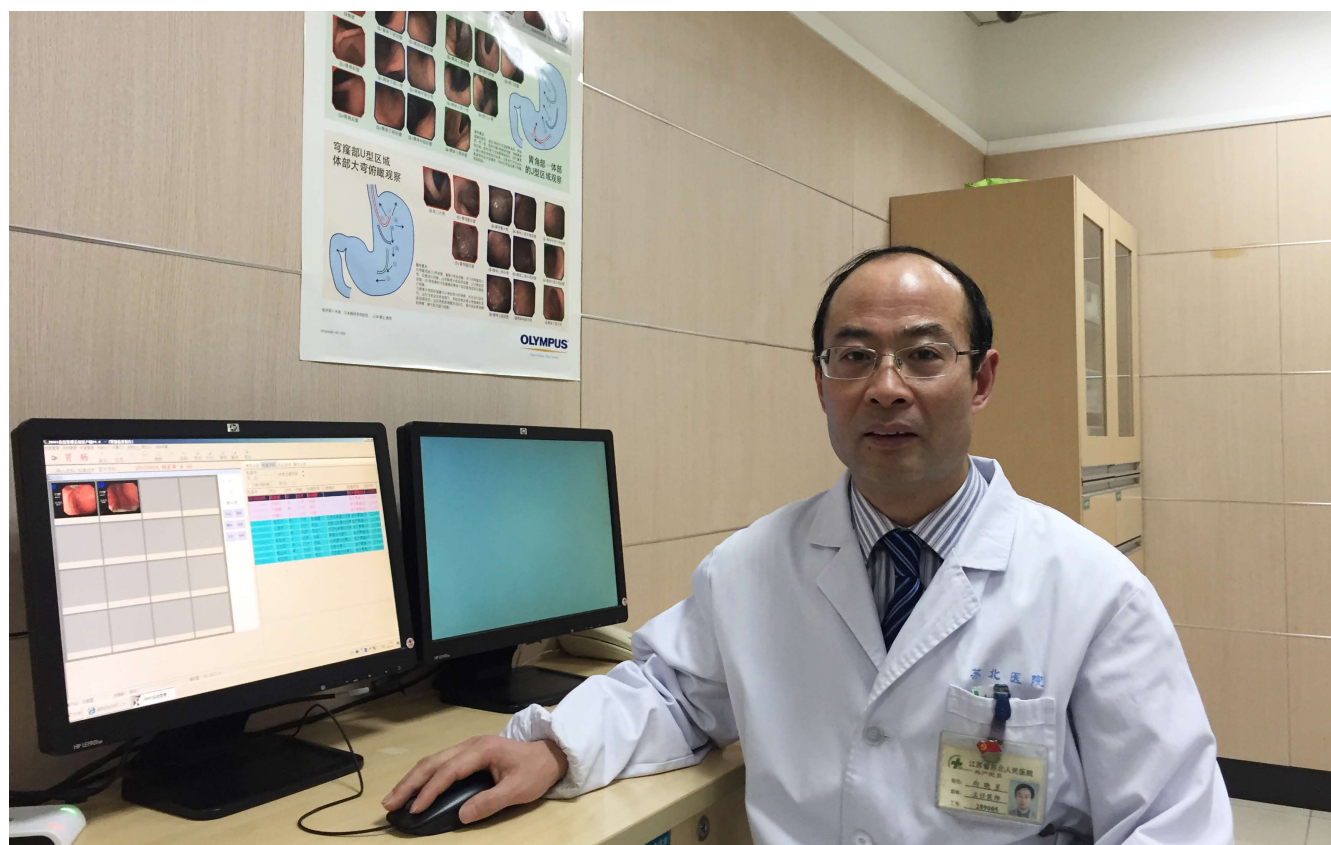


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封面故事

《世界华人消化杂志》编委, 向晓星, 主任医师, 博士, 硕士生导师, 225001, 江苏省扬州市南通西路98号, 苏北人民医院/扬州大学临床医学院消化内科. 现任消化内科副主任, 肝胆胰内科主任. 主要致力于肝脏疾病的基础与临床研究. 研究方向包括肝硬化食管胃静脉曲张破裂出血的内镜治疗, 原发性肝癌、自身免疫性肝病、脂肪性肝病的免疫学发病机制及治疗, 超声引导下肝脏良恶性肿瘤的微创治疗. 2005年获得上海第二医科大学内科学博士学位. 江苏省“333工程”首批中青年学术技术带头人, 扬州市消化病学学术技术带头人.

本期责任人

编务 李香; 送审编辑 闫晋利; 组版编辑 闫晋利; 英文编辑 王天奇; 责任编辑 马亚娟; 形式规范审核编辑部主任 马亚娟; 最终清样审核总编辑 马连生

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主编

程英升, 教授, 200233, 上海市, 上海交通大学附属第六人民医院放射科

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制作

北京百世登生物医学科技有限公司
100025, 北京市朝阳区东四环中路62号, 远洋国际中心D座903室

电话: 010-85381892

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COVER

Editorial Board Member of *World Chinese Journal of Digestology*, Xiao-Xing Xiang, Chief Physician, Department of Internal Medicine, Subei People's Hospital/Clinical Medical College of Yangzhou University, 98 Nantong West Road, Yangzhou 225001, Jiangsu Province, China

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EDITOR-IN-CHIEF

Ying-Sheng Cheng, Professor, Department of Radiology, Sixth People's Hospital of Shanghai Jiaotong University, Shanghai 200233, China

Shuang-Suo Dang, Professor, Department of Infectious Diseases, the Second Affiliated Hospital of Medical School of Xi'an Jiaotong University, Xi'an 710004, Shaanxi Province, China

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Zhan-Ju Liu, Professor, Department of Gastroenterology, Shanghai Tenth People's Hospital, Tongji University, Shanghai 200072, China

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EDITORIAL OFFICE

Ya-Juan Ma, Director
World Chinese Journal of Digestology
Baishideng Publishing Group Inc
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Fax: +1-925-223-8242
Telephone: +1-925-223-8243
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<http://www.wjgnet.com>

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PRODUCTION CENTER

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结直肠腺瘤上皮内瘤变高危因素657例分析

李加欢, 王立宇, 宋祥铭, 刘劲松

李加欢, 刘劲松, 华中科技大学同济医学院附属协和医院消化科
湖北省武汉市 430022

王立宇, 华中科技大学同济医学院附属协和医院肝胆外科 湖北省
武汉市 430022

宋祥铭, 华中科技大学同济医学院附属协和医院影像医学系 湖北省
武汉市 430022

李加欢, 医学硕士, 主要从事消化系统疾病临床诊治的相关研究.

作者贡献分布: 李加欢与王立宇对此课题所作贡献均等, 共同负责课题设计与病例数据分析; 数据收集由宋祥铭完成; 论文写作由李加欢与刘劲松共同完成.

通讯作者: 刘劲松, 教授, 主任医师, 博士生导师, 430022, 湖北省武汉市解放大道1227号, 华中科技大学同济医学院附属协和医院消化科.
jsliuxh@126.com
电话: 027-87543437

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Risk factors for intraepithelial neoplasia in patients with colorectal adenoma

Jia-Huan Li, Li-Yu Wang, Xiang-Ming Song, Jing-Song Liu

Jia-Huan Li, Jing-Song Liu, Department of Gastroenterology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, Hubei Province, China

Li-Yu Wang, Department of Hepatobiliary Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, Hubei Province, China

Xiang-Ming Song, Department of Medical Imaging, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, Hubei Province, China

Correspondence to: Jing-Song Liu, Professor, Chief Physician, Department of Gastroenterology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang

Avenue, Wuhan 430022, Hubei Province, China. jsliuxh@126.com

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Abstract

AIM

To identify risk factors for intraepithelial neoplasia in colorectal adenoma by analyzing the clinical, endoscopic, and histopathological features of patients with colorectal adenoma.

METHODS

The clinical, endoscopic, and histopathological features of 657 patients with colorectal adenomatous polyps diagnosed by colonoscopy from January 2014 to April 2016 at Wuhan Union Hospital were retrospectively analyzed. The patients were divided into an intraepithelial neoplasia group and a non-intraepithelial neoplasia group according to the pathological diagnosis. χ^2 test was applied for univariate analysis between the two groups. Multivariate Logistic regression analysis was used to identify the risk factors for intraepithelial neoplasia and its malignancy degree in adenoma.

RESULTS

Most of colorectal adenomas were located in the left colon. The total incidence of intraepithelial neoplasia in colorectal adenoma was 22.68%. Age, polyp diameter, length of pedicle, and pathologic type were identified to be risk factors for intraepithelial neoplasia in adenoma, which could be incorporated in Logistic regression equation: $\text{logit } P = -4.384 + 0.796X_2$ (age) + $0.324X_3$ (polyp diameter) + $1.296X_4$ (pedicle condition) + $0.944X_7$ (pathology type). Gender, age, and polyp size were identified to be risk factors for high-grade intraepithelial neoplasia in adenoma, which

could be incorporated in Logistic regression equation: $\text{logit } P = -2.939 + 1.036X_1 (\text{gender}) + 0.853X_2 (\text{age}) + 1.023X_3 (\text{polyp diameter})$. Total cholesterol (TC) and triglyceride (TG) in the low-grade and high-grade intraepithelial neoplasia groups were both significantly higher than those in the non-intraepithelial neoplasia group ($P < 0.05$). Low-density lipoprotein cholesterol (LDL-C) and uric acid (URIC) in the high-grade intraepithelial neoplasia group were both significantly higher than those in the non-intraepithelial neoplasia group ($P < 0.05$). There was no significant difference in the high-density lipoprotein cholesterol (HDL-C) or CEA among the three groups.

CONCLUSION

There is a greater risk of intraepithelial neoplasia among patients older than 40, having villous adenoma with diameter > 1 cm and pedicle. Male, polyp diameter, and age are risk factors for high-grade intraepithelial neoplasia in colorectal adenoma. The occurrence of intraepithelial neoplasia in adenoma may be related to blood lipids and uric acid levels.

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Key Words: Colorectal adenoma; Intraepithelial neoplasia; Endoscopy; Serum lipids; Risk factors

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摘要

目的

分析结直肠腺瘤临床、内镜及病理组织学特点, 总结结直肠腺瘤发生上皮内瘤变的相关危险因素。

方法

回顾分析华中科技大学同济医学院附属协和医院2014-01/2016-04以电子结肠镜检出并经病理证实为结直肠腺瘤性息肉的657例患者的相关临床资料, 依据是否存在上皮内瘤变分为上皮内瘤变组和非上皮内瘤变组, 组间采用 χ^2 检验, 腺瘤发生上皮内瘤变及其恶变程度的相关危险因素采用多因素Logistic回归分析。

结果

结直肠腺瘤多发生于左半结肠, 上皮内瘤变总发生率为22.68%, 年龄、息肉直径、蒂的长度、病理类型是腺瘤上皮内瘤变的危险因素, 可纳入Logistic回归方程: $\text{logit } P = -4.384 + 0.796X_2 (\text{年龄}) + 0.324X_3 (\text{息肉直径}) + 1.296X_4 (\text{蒂部形态}) + 0.944X_7 (\text{病理类$

型)。性别、年龄、息肉大小是腺瘤高级别内瘤变的危险因素, 可纳入Logistic回归方程: $\text{logit } P = -2.939 + 1.036X_1 (\text{性别}) + 0.853X_2 (\text{年龄}) + 1.023X_3 (\text{息肉直径})$ 。低级别及高级别上皮内瘤变组总胆固醇、甘油三酯水平均显著高于无上皮内瘤变组($P < 0.05$)。高级别上皮内瘤变组在低密度脂蛋白、尿酸(uric acid, URIC)均显著高于无上皮内瘤变组($P < 0.05$)。而三组之间高密度脂蛋白、癌胚抗原无明显差异。

结论

年龄 > 40 岁、直径 > 1 cm、有蒂及绒毛管状腺瘤更易发生上皮内瘤变, 男性、息肉直径、年龄是结直肠腺瘤发生高级别上皮内瘤变的危险因素。结直肠腺瘤发生上皮内瘤变可能与血脂、URIC水平有关。

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关键词: 结直肠腺瘤; 上皮内瘤变; 内镜; 血脂; 危险因素

核心提要: 本研究总结腺瘤性息肉上皮内瘤变患者的临床特征, 发现患者年龄 > 40 岁或腺瘤直径 > 1 cm、有蒂及绒毛管状腺瘤更易发生上皮内瘤变, 男性、息肉直径、年龄是结直肠腺瘤发生高级别上皮内瘤变的危险因素, 结直肠腺瘤发生上皮内瘤变可能与血脂、尿酸水平有关, 对临床工作有一定指导意义。

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0 引言

结直肠癌是最常见的恶性肿瘤之一, 在世界范围内均有较高的发病率和死亡率^[1]。约80%以上的结直肠癌^[2,3]都是由结直肠腺瘤发展而来, 及时发现被摘除结直肠腺瘤可降低75%以上的结肠癌的发生率^[4]。而目前研究^[2,5]认为传统腺瘤主要通过发生上皮内瘤变逐渐发展为腺癌, 因此上皮内瘤变被视为结直肠癌重要的癌前病变。发生高级别上皮内瘤变的结直肠腺瘤癌变几率相对更高^[6]。早期发现可能发生上皮内瘤变的高危腺瘤性息肉患者并进行积极治疗可有效预防结直肠腺瘤癌变的发生, 本研究拟总结腺瘤性息肉上皮内瘤变患者的临床特征, 以提高上皮内瘤变的检出水平, 促进对结肠癌的诊治。

1 材料和方法

1.1 材料 本研究入组病例来源于2014-01/2016-04华中科技大学同济医学院附属协和医院治疗结直肠腺瘤的住

表 1 结直肠腺瘤不同性别、年龄、大小、蒂部、部位、数量、病理的比较

项目	无上皮内瘤变	有上皮内瘤变		上皮内瘤变发生率(%)	χ^2_1	χ^2_2	P_1	P_2
		低级别	高级别					
性别					0.477	2.244	0.490	0.134
男	389	44	66	22.04				
女	119	21	18	24.68				
年龄(岁)								
<40	26	3	0	10.34				
40-59	314	40	36	19.49	1.475	1.050	0.225	0.305 ^a
≥60	168	22	48	29.41	248.726	3.348	0.000	0.067 ^a
直径 (cm)								
≤1	464	55	26	14.86				
>1	44	10	58	60.71	111.39	42.534	0.000	0.000
蒂部情况								
无蒂	299	13	19	9.67				
亚蒂	171	16	20	17.39	6.88	0.101	0.009	0.751 ^c
有蒂	38	36	45	68.07	158.744	0.136	0.000	0.712 ^c
部位								
左半结肠	359	49	62	23.62				
右半结肠	149	16	22	20.32	0.829	0.048	0.363	0.827
息肉数目								
单发	193	24	31	22.18				
多发	315	41	53	22.98	0.057	0.000	0.811	0.998
病理类型								
管状	415	30	16	9.98				
绒毛状	39	14	10	38.1	37.858	0.320	0.000	0.572 ^e
绒毛-管状	54	21	58	59.4	151.728	17.966	0.000	0.000 ^e

^a $P<0.05$ vs <40岁组; ^c $P<0.05$ vs 无蒂组; ^e $P<0.05$ vs 管状腺瘤组. χ^2_1 , P_1 为无上皮内瘤变组与有上皮内瘤变组相比; χ^2_2 , P_2 为低级别上皮内瘤变组与高级别上皮内瘤变组相比.

院患者, 排除既往有结直肠恶性肿瘤病史(15例)、家族性增生性息肉病史(1例)、肠道清洁程度较差者(8例)、既往摘除肠道息肉病史患者(38例), 按时间顺序最终入组657例患者. 所有病例均经电子结肠镜和病理组织学检查确诊为结肠腺瘤性息肉. 其中男499例, 女158例, 年龄12-84岁, 平均年龄55.38岁±12.61岁, 所有息肉均通过结肠镜下完全切除, 术后全部标本送检.

1.2 方法 患者于华中科技大学同济医学院附属协和医院完善心电图、血常规、血脂、肝肾功能、癌胚抗原(carcino-embryonic antigen, CEA)等检查, 签署知情同意书后, 经严格的肠道准备后, 采用电子结肠镜检查: 插镜至回盲部, 然后缓慢退镜的同时进行全结肠观察, 明确息肉解剖部位、测量大小、数量及观察基蒂特征, 并行内镜下黏膜剥离切除术(endoscopic mucosal resection, EMR)或者内镜黏膜下剥离术(endoscopic submucosal dissection, ESD), 完整切除标本全部送常规病理检查. 需收集的临床数据包括患者年龄、性别、家族史, 内镜数据包括息肉大小、位置、数量、形态,

病理数据包括息肉病理类型及有无上皮内瘤变. 根据世界卫生组织定义低级别上皮内瘤变包括轻、中度异型增生, 高级别上皮内瘤变则包括重度异型增生、原位癌、原位癌可疑浸润以及黏膜内癌. 结直肠腺瘤病理类型包括: 管状腺瘤、绒毛状腺瘤和管状绒毛状腺瘤. 分组: 按病理结果分为有上皮内瘤变组及无上皮内瘤变组. 有上皮内瘤变组, 根据腺瘤恶变程度分为高级别上皮内瘤变组及低级别上皮内瘤变组.

统计学处理 应用SPSS19.0对数据进行统计分析, 正态计量资料用mean±SE表示, 计数资料组间比较采用 χ^2 检验, 腺瘤发生上皮内瘤变及其程度的相关危险因素采用多因素Logistic回归分析, 进入变量的显著性水准取0.05, 剔除变量的显著性水准取0.10. $P<0.05$ 为差异具有统计学意义.

2 结果

2.1 结肠腺瘤临床病理特征与腺瘤发生率 657例结肠腺瘤病例临床、内镜、病理资料如表1, 其中149例经

表 2 Logistic回归自变量和因变量赋值说明

变量	赋值
X1: 性别	女 = 0, 男 = 1
X2: 年龄	<40岁 = 0, 40–59岁 = 1, ≥60岁 = 2
X3: 息肉直径	≤0.5 cm = 0, 0.6–1.0 cm = 1, 1.1–2.0 cm = 2, >2.0 cm = 3
X4: 蒂部形态	无蒂 = 0, 亚蒂 = 1, 有蒂 = 2
X5: 生长部位	右半结肠 = 0, 左半结肠 = 1
X6: 息肉数目	单发 = 0, 多发 = 1
X7: 病理类型	管状腺瘤 = 0, 绒毛状腺瘤 = 1, 绒毛管状腺瘤 = 2
Y1: 有无上皮内瘤变	无上皮内瘤变 = 0, 有上皮内瘤变 = 1
Y2: 发生上皮内瘤变程度	低级别上皮内瘤变 = 0, 高级别上皮内瘤变 = 1

表 3 结直肠腺瘤发生上皮内瘤变多因素Logistic回归分析

因素	回归系数	标准误	Wals	P值	OR值	95%CI
年龄	0.796	0.239	11.057	0.001	2.217	1.387–3.544
病理类型	0.944	0.163	33.394	0.000	2.571	1.866–3.541
大小	0.324	0.168	3.733	0.053	1.382	0.995–1.92
蒂部	1.296	0.161	64.445	0.000	3.654	2.663–5.015
常量	-4.384	0.437	100.584	0.000	0.012	

表 4 结直肠腺瘤发生上皮内瘤变程度多因素Logistic回归分析

因素	回归系数	标准误	Wals	P值	OR值	95%CI
性别	1.036	0.471	4.837	0.028	2.817	1.119–7.089
年龄	0.853	0.391	4.755	0.029	2.347	1.09–5.055
大小	1.023	0.213	23.044	0.000	2.782	1.832–4.225
常量	-2.939	0.810	13.169	0.000	0.053	

病理证实发生了上皮内瘤变(腺瘤上皮内瘤变发生率为22.68%), 其中发生高级别上皮内瘤变者84例(腺瘤高级别上皮内瘤变发生率为12.78%)。管状、绒毛状、绒毛管状腺瘤平均直径为: 5.37 mm±4.89 mm, 11.34 mm±10.52 mm, 14.52 mm±10.58 mm。无上皮内瘤变组、低级别及高级别上皮内瘤变组腺瘤平均直径分别为: 4.58 mm±4.80 mm, 8.58 mm±8.21 mm, 13.76 mm±12.54 mm。

比较无上皮内瘤变与伴有上皮内瘤变组, 各年龄层、不同直径息肉组间、不同蒂部、三种病理类型(管状、绒毛状、绒毛管状腺瘤)的腺瘤上皮内瘤变发生率 χ^2 检验提示有统计学差异($P<0.05$), 结直肠腺瘤上皮内瘤变发生率在性别、左右半结肠、息肉发生数量之间无显著差异(表1)。

比较低级别上皮内瘤变与高级别上皮内瘤变组, 各年龄层、不同直径息肉组、不同病理类型(管状、绒毛状、绒毛管状腺瘤)的结直肠腺瘤恶变程度经 χ^2

检验有统计学差异($P<0.05$), 但在男女、有无蒂部及蒂部形态、部位、单发多发组间无显著差异(表1)。

2.2 结直肠腺瘤上皮内瘤变危险因素分析 多因素Logistic回归分析(赋值说明如表2)显示年龄、息肉病理类型、直径、有无蒂部及蒂部形态是结直肠腺瘤发生上皮内瘤变的危险因素(表3), 可纳入Logistic回归方程: $\text{logit } P = -4.384 + 0.796X_2(\text{年龄}) + 0.324X_3(\text{息肉直径}) + 1.296X_4(\text{蒂部形态}) + 0.944X_7(\text{病理类型})$ 。

2.3 结直肠腺瘤高级别内瘤变危险因素分析 多因素Logistic回归分析(赋值说明如表2)显示性别、年龄、息肉大小是腺瘤性息肉发生高级别上皮内瘤变的危险因素(表4), 可纳入Logistic回归方程: $\text{logit } P = -2.939 + 1.036X_1(\text{性别}) + 0.853X_2(\text{年龄}) + 1.023X_3(\text{息肉直径})$ 。

2.4 结直肠腺瘤患者代谢相关指标及肿瘤标志物 657例结直肠腺瘤患者血脂、尿酸(uric acid, URIC)、CEA水平如表5, 经3组间数据方差齐检验低级别及高级别

表 5 结直肠腺瘤患者血浆TC、TG、HDL-C、LDL-C、URIC、CEA水平比较 (mean ± SD)

分组	n	TC (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	URIC (μmol/L)	CEA (μg/L)
无上皮内瘤变	508	3.81 ± 0.81	0.95 ± 0.61	1.26 ± 0.26	2.01 ± 0.64	300.71 ± 59.10	2.55 ± 1.38
低级别上皮内瘤变	65	4.35 ± 0.95	1.46 ± 1.09	1.32 ± 0.26	2.34 ± 0.77	340.26 ± 75.36	2.50 ± 1.57
高级别上皮内瘤变	84	4.72 ± 0.76 ^a	1.52 ± 0.76 ^a	1.34 ± 0.26	2.71 ± 0.85 ^a	363.76 ± 118.11 ^a	2.60 ± 1.51

^a $P < 0.05$ vs 低级别上皮内瘤变组. TC: 总胆固醇; TG: 甘油三酯; HDL-C: 高密度脂蛋白; LDL-C: 低密度脂蛋白; URIC: 尿酸; CEA: 癌胚抗原.

上皮内瘤变组总胆固醇(total cholesterol, TC)、甘油三酯(triglyceride, TG)水平均显著高于无上皮瘤变组($P < 0.05$). 高级别上皮瘤变组低密度脂蛋白(low-density lipoprotein cholesterol, LDL-C)、URIC均与无上皮内瘤变组有显著差异($P < 0.05$). 而3组之间高密度脂蛋白(high-density lipoprotein cholesterol, HDL-C)、CEA水平无显著差异.

3 讨论

随着内镜技术的发展, 结直肠息肉的检出率大幅提高, 约50%-76%为腺瘤性息肉^[7,8], 其中约有1/5的腺瘤性息肉可发展为结直肠腺癌. 根据Morson^[2]提出的结肠息肉-腺瘤-腺癌的演变学说理论, 腺瘤性息肉从发生至癌变的过程约10年左右, 但已上皮内瘤变的腺瘤发展为腺癌的时间约为1-3年. 因此及时发现上皮内瘤变可有效降低结直肠腺癌的发生率, 提高患者生活质量.

本研究657例患者中, 男女患者比例约为3.15:1, 结直肠腺瘤上皮内瘤变发生率及瘤变程度两者之间无统计学差异. 对腺瘤上皮内瘤变程度进行Logistic回归分析发现男性是结直肠腺瘤发生高级别上皮内瘤变的危险因素($OR = 2.817$, 95%CI: 1.119-7.089, $P < 0.05$), Fort Gasia等^[9]研究认为这与男性抽烟、饮酒比例高于女性有关. 年龄是结直肠腺瘤恶变的危险因素, 这一观点与Siegel等^[10]的观点相互印证, 年龄在多项研究中^[11-13]也被证实为结直肠癌明确的危险因素. 本研究进一步证明随着结直肠腺瘤患者年龄增高, 发生上皮内瘤变可能性增大($OR = 2.217$, 95%CI: 1.387-3.544, $P < 0.001$), 同时发生高级别上皮内瘤变可能性亦显著提高($OR = 2.347$, 95%CI: 1.09-5.055, $P < 0.05$). 值得注意的是本研究中统计结果显示40岁以上结直肠腺瘤患者中上皮内瘤变发生率高达23.25%, 这与我国成人结直肠癌发生年龄基本一致, 进一步证实目前我国的专家共识^[14]呼吁将结直肠癌的筛查年龄提前至40岁是非常必要之举.

3组腺瘤中, 无上皮内瘤变的腺瘤直径多 < 1 cm, 而高级别瘤变腺瘤常 > 1 cm, 部分 > 2 cm. 多因素回归分析结果显示腺瘤发生上皮内瘤变与瘤体体积相关, 直

径 > 1 cm者相比 < 1 cm者更易发生恶变, 且发生高级别上皮内瘤风险更高($OR = 2.782$, 95%CI: 1.832-4.225, $P < 0.001$), 与Kim等^[15]及Ahlawat等^[16]研究结果一致. 同时, 息肉带蒂是结直肠腺瘤发生上皮内瘤变的危险因素($OR = 3.654$, 95%CI: 2.663-5.015, $P < 0.001$), 其中有蒂腺瘤2/3以上发生了上皮内瘤变, 考虑有蒂腺瘤病理类型常为绒毛状或绒毛-管状, 且体积偏大, 因此上皮内瘤变发生率. 管状腺瘤是最常见的腺瘤类型, 在本研究中发生率达70.17%, 与既往研究^[17]相近. 绒毛状腺瘤及绒毛管状腺瘤平均体积大于管状腺瘤, 发生上皮内瘤变比例明显高于管状腺瘤, 其中绒毛管状腺瘤上皮内瘤变率高达59.4%, 考虑与腺瘤体积大小及绒毛组织成分含量相关. Toll等^[18]研究证实绒毛组织越多, 腺瘤越易发生恶变. 含有绒毛组织的腺瘤已被视为进展期腺瘤^[19], 但发生机制仍需进一步研究.

内镜下检出结直肠腺瘤多见于左半结肠, 占总数71.54%, 与既往报道相近^[7,18], 因此电子肠镜检查时应重点关注左半结肠, 但本研究显示腺瘤发生上皮内瘤变及恶变程度在左右半结肠分布无显著差异.

多项研究证实结直肠腺瘤发生、发展及恶变与代谢因素相关^[19,20]. 本研究结果发现已发生上皮内瘤变结肠腺瘤患者TC及TG水平较高, 与既往国内外研究一致^[21,22]. 血浆TC及TG增高可能促进结肠腺瘤恶变, 考虑可能与高脂饮食有关. Fang等^[23]研究认为高脂饮食促进胆汁分泌, 在肠道菌群的作用下诱导肠道上皮细胞及腺瘤细胞异常增殖从而促进结肠腺瘤的发生发展. 本研究中高级别上皮内瘤变组LDL-C、URIC水平均显著高于无上皮内瘤变组. LDL-C增高可增加脂质的氧化从而促进肠上皮细胞异常增殖, Jung等^[24]认为高水平LDL-C可使进展期结肠腺瘤发生风险增加1.83倍(95%CI: 1.23-1.54). 研究结果中未显示HDL-C水平与结肠腺瘤发生上皮内瘤变间有相关性, 与Kim等^[22]研究一致, 但与其他研究^[25,26]存在差异, 因此关于HDL-C与结直肠腺瘤的相关性尚存在争论. 本研究显示高URIC血症可能增加结直肠腺瘤上皮内瘤变的发生, 已有研究^[27,28]认为高水平URIC可能参与肿瘤的发生.

本研究中, 3组腺瘤中, CEA无统计学差异, 提示血清CEA对于反映在结肠腺瘤发生上皮内瘤变敏感性低, 对疾病进展的指示性不强. CEA常用于大肠癌的病情发展监测及预后评估, 但其受敏感性限制对肠道肿瘤的早期诊断作用不突出.

总之, 对于息肉发生在左半结肠、年龄在40岁以上(尤其是60岁以上)患者, 如果息肉直径>1 cm、带蒂, 需我们在进行内镜检查及治疗时给予更多的重视, 避免漏诊可能发生的癌前病变, 应尽可能完整的切除息肉并进行病理检查, 同时需监测患者血脂、URIC等指标的情况, 建议患者合理膳食, 降低血脂、URIC等, 以期能尽早阻断腺瘤的发生途径, 降低结肠癌的发生率.

文章亮点

实验背景

结直肠腺瘤是最常见的结肠息肉, 容易恶变. 目前认为结直肠腺瘤主要通过发生上皮内瘤变逐渐发展为腺癌, 因此上皮内瘤变被视为结直肠癌重要的癌前病变.

实验动机

及时发现可能发生上皮内瘤变的高危腺瘤性息肉的患者, 并进行积极治疗可有效预防结直肠腺瘤癌变的发生.

实验目标

分析结直肠腺瘤临床、内镜及病理组织学特点, 总结结直肠腺瘤发生上皮内瘤变的相关危险因素.

实验方法

本研究回顾分析657例结直肠腺瘤患者的相关临床资料, 总结腺瘤性息肉上皮内瘤变患者的临床特征.

实验结果

结直肠腺瘤多发生于左半结肠, 年龄、息肉直径、蒂的长度、病理类型是腺瘤上皮内瘤变的危险因素, 性别、年龄、息肉大小是腺瘤高级别内瘤变的危险因素. 低级别及高级别上皮内瘤变组总胆固醇、甘油三酯水平均显著高于无上皮内瘤变组. 高级别上皮瘤变组在低密度脂蛋白、尿酸均显著高于无上皮内瘤变组. 而三组之间高密度脂蛋白、癌胚抗原无明显差异.

实验结论

发现患者年龄>40岁或腺瘤直径>1 cm、有蒂及绒毛管状腺瘤更易发生上皮内瘤变, 男性、息肉直径、年龄是结直肠腺瘤发生高级别上皮内瘤变的危险因素, 结直肠腺瘤发生上皮内瘤变可能与血脂、尿酸水平有关.

展望前景

此研究对提高腺瘤上皮内瘤变的检出水平, 防治结肠癌有一定临床价值.

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