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MiRNA-146a rs2910164基因多态性与大肠癌易感性的系统评价

谢文群, 谭诗云, 王晓凡

■背景资料
大肠癌是重要的全球性公共卫生问题, 尽管大肠癌的病因虽未明确, 但其相关的高危因素渐被认识, 遗传易感性与大肠癌的发生发展密切相关. 位于miR-146a前体pre-miRNA茎环结构区域的一个G/C单核苷酸多态性(miR-146a rs2910164)可以导致miR-146a的表达异常, 进而导致肿瘤的发生发展.

谢文群, 谭诗云, 王晓凡, 武汉大学人民医院消化内科 湖北省武汉市 430060
谢文群, 武汉大学人民医院研究生, 主要从事消化内镜诊治优化的研究.
作者贡献分布: 谢文群及王晓凡对此文所做贡献均等; 此课题由谭诗云教授设计; 文献检索及数据搜集、分析过程由谢文群及王晓凡完成; 本论文写作由谢文群完成.
通讯作者: 谭诗云, 主任医师, 博士生导师, 430060, 湖北省武汉市武昌紫阳路99号, 武汉大学人民医院消化内科.
tanshiyun@medmail.com.cn
电话: 027-88041911-82145
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Association between miRNA-146a rs2910164 gene polymorphism and susceptibility to colorectal cancer: A systematic review

Wen-Qun Xie, Shi-Yun Tan, Xiao-Fan Wang

Wen-Qun Xie, Shi-Yun Tan, Xiao-Fan Wang, Department of Gastroenterology, Renmin Hospital of Wuhan University, Wuhan 430060, Hubei Province, China
Correspondence to: Shi-Yun Tan, Chief Physician, Department of Gastroenterology, Renmin Hospital of Wuhan University, 99 Wuchang Ziyang Road, Wuhan 430060, Hubei Province, China. tanshiyun@medmail.com.cn
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Abstract

AIM: To accurately evaluate the association between the miRNA-146a rs2910164G/C polymorphism and susceptibility to colorectal cancer.

METHODS: An electronic search of PubMed, Excerpta Medica Database (Embase), Chinese Biomedical Literature Database (CBM), the Cochrane Library, Weipu and Wanfang Database was performed to collect all the publications investigating the association between miR-146a rs2910164G/C polymorphism and risk of colorectal cancer. We then analyzed the differences in miRNA-146a rs2910164G/C genotypes (G *vs* C, GG *vs* CC, GG *vs* GC, GC *vs* CC, GG + GC *vs* CC, GG *vs* GC + CC) between cases and controls by meta-analysis.

RESULTS: Seven studies involving 2978 cases and 3576 controls were found to be eligible for meta-analysis. We summarized the data on the association between miR-146a rs2910164G/C polymorphism and risk of colorectal cancer in the overall population. In the overall analysis, there was no evidence for an association between the miR-146a rs2910164 polymorphism and the risk of colorectal cancer (G *vs* C: OR = 0.82, 95%CI: 0.52-1.30, *P* = 0.41; GG *vs* CC: OR = 1.10, 95%CI: 0.72-1.40, *P* = 0.97; GG *vs* GC: OR = 1.10, 95%CI: 0.81-1.28, *P* = 0.91; GC *vs* CC: OR = 0.99, 95%CI: 0,70-1.41, *P* = 0.96; GG + GC *vs* CC: OR = 1.00, 95%CI: 0.72-1.39, *P* = 0.99; GG *vs* GC + CC: OR = 1.00, 95%CI: 0.81-1.24, *P* = 0.98).

CONCLUSION: This meta-analysis demonstrated that the miR-146a rs2910164 polymorphism is not associated with colorectal cancer susceptibility.

Key Words: MicroRNA; Single nucleotide polymorphisms; Colorectal cancer; Meta-analysis

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摘要

目的: 评价miRNA-146a rs2910164 G/C基因多态性与大肠癌易感性的相关性.

方法: 全面检索Pubmed、Excerpta Medica Database (Embase)、Chinese Biomedical Literature Database (CBM)and the Cochrane Library、维普、万方数据库, 收集研究miRNA-146a rs2910164 G/C基因多态性与大

■同行评议者
王道荣, 主任医师, 江苏省苏北人民医院胃肠外科

肠癌易感性相关性的文献. 对miRNA-146a rs2910164 G/C各基因型的比较模型(G *vs* C、GG *vs* CC、GG *vs* GC、GC *vs* CC、GG + GC *vs* CC、GG *vs* GC + CC)进行定量综合分析.

结果: 共纳入7篇文献, 共有大肠癌患者2978例, 健康对照3576例. Meta分析尚未发现miRNA-146a rs2910164 G/C基因多态性与大肠癌易感性具有相关性(G *vs* C: OR = 0.82, 95%CI: 0.52-1.30, *P* = 0.41; GG *vs* CC:OR = 1.10, 95%CI: 0.72-1.40, *P* = 0.97; GG *vs* GC: OR = 1.10, 95%CI: 0.81-1.28, *P* = 0.91; GC *vs* CC: OR = 0.99, 95%CI: 0.70-1.41, *P* = 0.96; GG + GC *vs* CC: OR = 1.00, 95%CI: 0.72-1.39, *P* = 0.99; GG *vs* GC + CC: OR = 1.00, 95%CI: 0.81-1.24, *P* = 0.98).

结论: 本研究尚未发现miRNA-146a rs2910164 G/C基因多态性与大肠癌易感性之间具有相关性.

关键词: MiRNA; **基因多态性**; **大肠癌**; Meta分析

核心提示: 单核苷酸多态性(single nucleotide polymorphism, SNP)是最常见的基因变异, 他与种族差异、疾病易感性及药物反应差异有关. 本次研究首次采用Meta分析的方法综合评价miR-146a rs2910164G/C基因多态性与大肠癌易感性之间的相关性.

谢文群, 谭诗云, 王晓凡. MiRNA-146a rs2910164 基因多态性与大肠癌易感性的系统评价. 世界华人消化杂志 2014; 22(6): 890-897 URL: http://www.wjgnet.com/1009-3079/22/890.asp DOI: http://dx.doi.org/10.11569/wcjd.v22.i6.890

0 引言

据2011年全球癌症统计显示: 全球每年约有1200000例新发大肠癌病例和608700例死亡病例, 大肠癌的发病率居女性所有恶性肿瘤的第2位; 居男性所有恶性肿瘤的第3位, 其死亡率居分别居女性及男性所有恶性肿瘤死亡率的第3、4位. 大肠癌已成为重要的全球性公共卫生问题[1,2]. 尽管大肠癌的病因虽未明确, 但其相关的高危因素渐被认识, 如吸烟、嗜酒、体力活动不足、肥胖及遗传易感性等[3,4]. 在这些危险因素中, 遗传易感性与大肠癌的发生发展密切相关[5].

微小RNA(microRNA, miRNA)是存在于真核细胞当中具有进化保守性的一族非编码小片段RNA, 大小为18-24 bp, 通过与靶基因mRNA的碱基互补配对来影响mRNA的稳定性或抑制其翻译, 实现对蛋白表达的调控[6]. MiRNA调控着大约30%的人类基因的转录体[7], 控制着细胞的分化、增殖和程序性细胞死亡等多种重要生理及病理过程[8]. 最近研究发现, miRNA具有类似癌基因或抑癌基因的功能[9,10], 并且, miRNA在正常细胞和癌细胞中表达不同, 几乎所有的肿瘤都存在miRNA的表达异常[11,12]. miRNA的表达具有组织特异性, 其表达谱与肿瘤的特点、分级相关, 在一些未发现原发灶的肿瘤疾病中miRNA可以用来判断肿瘤组织的来源[13,14]. 因此, miRNA对肿瘤的诊断、治疗及预后都有重要意义. 作为最常见且重要的遗传标记, 单核苷酸多态性(single nucleotide polymorphism, SNP)是指DNA序列单个核苷酸的变异, 其在特定的人群中发生率至少为1%. 单核苷酸多态性与多种癌症的病因及预后相关[15-23]. 研究发现, 位于miRNA前体(pre-miRNAs)或成熟miRNA中的单核苷酸多态性会导致miRNA表达量及其功能的改变, 最终导致癌症等疾病的发生发展[24,25]. MiR-146a位于人类基因组的5q33, 其在多种实体瘤中表达异常. 研究发现, 位于miR-146a前体pre-miRNA茎环结构区域的一个G/C单核苷酸多态性(miR-146a rs2910164)可以导致miR-146a的表达异常, 进而导致肿瘤的发生发展[26-34]. 近年来, 国内外对miR-146a rs2910164基因多态性是否与大肠癌的发病有关进行了研究[35-41], 但是, 单个研究间结果不尽一致, 为此, 本研究应用Meta分析的方法对以往研究结果进行定量合并与综合评价, 进一步探讨miR-146a rs2910164基因多态性与大肠癌易感性之间的相关性.

1 材料和方法

1.1 材料 由2名独立研究者对文献进行系统的检索, 任何分歧都通过双方的讨论达成一致. 以“miR-146a”、“rs2910164”、“基因多态性”和“大肠癌”为主题词检索维普、万方数据资源系统、中国生物医学文献数据库(Chinese Biomedical Literature Database, CBM), 并以“miR-146a”、“rs2910164”、“gene”、“variants”、“alleles”、“mutation”、“polymorphism”和“colorectal cancer”检索Pubmed、Excerpta Medica Database(Embase)、

■研发前沿
单核苷酸多态性(single nucleotide polymorphism, SNP)是最常见的基因变异, 他与种族差异、疾病易感性及药物反应差异有关. 位于miRNA相关基因的单核苷酸多态性可以改变miRNA的表达量及功能, 进而导致肿瘤等疾病的发生. 近年来, 关于miR-146ars2910164基因多态性与大肠癌易感性的单个研究结果不尽一致; 且相关meta分析存在纳入文献较少的缺点.

■相关报道
Wang等系统评价了miR-146a rs2910164基因多态性与消化系统肿瘤易感性的相关性,本篇报道广泛搜集相关文献,所研究的消化系统肿瘤较全面.

表 1 纳入文献的基本情况

编号	研究	发表年限	种族	样本含量		H-W遗传平衡检验	质量评分
				病例组	对照组	*P*值	
1	Vinci等[35]	2013	高加索人	160	178	0.590	14
2	Ma等[36]	2013	亚洲人	1147	1203	0.075	15
3	Hezova等[37]	2012	高加索人	197	212	0.410	14
4	Chae等[38]	2013	亚洲人	399	568	0.950	15
5	Hu等[39]	2013	亚洲人	276	373	>0.05	15
6	Min等[40]	2012	亚洲人	446	502	0.443	15
7	Lv等[41]	2013	亚洲人	353	540	0.080	15

the Cochrane Library等数据库, 辅以文献追溯和手工检索等方法. 对miR-146a rs2910164基因多态性与大肠癌易感性关系的研究报道末次检索为2013-10, 未进行语种限定.

1.2 方法

1.2.1 文献纳入与排除标准: 纳入标准: (1)关于miR-146a rs2910164基因多态性与大肠癌易感性之间相关性的研究; (2)基于人的病例对照研究; (3)研究对象为病理组织学确诊的大肠癌患者; (4)各文献提供完整的病例组与对照组miR-146a rs 2910164的各基因型频数, 可计算比数比(odds ratio, OR)及其95%可信区间(confidence interval, 95%CI); (5)原始资料为已公开发表的中英文文献. 排除标准: (1)对同一研究重复发表的文献报道, 只选取近期发表和结果最完整的文献; (2)未提供充分原始数据的且索取无果; (3)只有摘要而缺乏全文. 当一篇文献对不同种族进行研究时, 则将每个种族的研究结果分别进行提取.

1.2.2 数据提取: 由2名独立的研究者对纳入文献的数据进行提取并核对, 任何分歧都通过双方讨论达成一致. 提取的主要内容包括第一作者姓名、发表年份、种族、病例组和对照组的样本量、等位基因及各基因型分布频数等.

1.2.3 文献质量评价: 由2名独立的研究者对纳入文献进行质量评价, 任何分歧都通过双方讨论达成一致. 评价标准为一组预先设定的标准. 该组标准是从以前的研究中提取的[42], 他以传统的流行病学及癌症的遗传问题为基础,该标准从5个方面对每个研究的质量进行评分.每个研究的得分是介于0到18的整数. 等于或大于12表明该文献质量好.

统计学处理 H-W遗传平衡检验: 对各研究的对照组人群基因型分布进行H-W遗传平衡检验, 计算卡方值,P<0.05为不符合H-W遗传平衡[43]. Meta分析: OR及95%CI作为评价指标, 评价miR-146a rs2910164基因多态性与大肠癌易感性的相关性. 分别计算每个miR-146a rs2910164 G/C基因模型的合并OR及其95%CI. 用Q检验和I^2检验探究各研究间的异质性, 若PQ<0.10, I^2>50%, 说明各研究间存在显著异质性, 则采用随机效应模型进行数据合并; 反之各研究间则不存在显著异质性, 用固定效应模型进行数据合并[44,45]. 用Begg's漏斗图及Egger's线性回归分析来估计潜在的发表偏倚[46,47], P>0.05为不存在发表偏倚.

2 结果

2.1 纳入研究的一般情况 初检出相关文献100篇, 均为英文文献, 经阅读问题及摘要后. 剔除93篇文献(36篇为Meta分析, 57篇为研究其他疾病), 进一步查找和阅读全文后, 剔除2篇文献(均为机制研究), 最后通过文献追溯的方法在Meta分析的参考文献中找到2篇符合标准的文献, 最终纳入7篇文献[35-41], 包含大肠癌患者2978例, 健康对照3576例. 纳入研究质量评分均>12, 表明纳入研究的质量较好. H-W遗传平衡检验结果显示对照组人群基因型分布符合H-W遗传平衡. 纳入研究的一般情况如表1, 文献筛选流程如图1所示.

2.2 Meta分析结果 对纳入研究进行Meta分析, 因纳入研究的各基因型均存在显著的异质性(I^2>50%), 故采用随机效应模型进行数据合并. 各基因型合并OR及其95%CI结果如表2所示: G *vs* C: OR = 0.82, 95%CI: 0.52-1.30, P = 0.41; GG *vs* CC: OR = 1.10, 95%CI: 0.72-1.40, P = 0.97; GG *vs* GC: OR = 1.10, 95%CI: 0.81-1.28, P = 0.91; GC *vs* CC: OR = 0.99, 95%CI: 0.70-1.41, P = 0.96; GG + GC *vs* CC: OR = 1.00, 95%CI: 0.72-1.39, P = 0.99; GG *vs* GC + CC: OR = 1.00,

表 2 miR-146a rs2910164基因多态性与大肠癌易感性的Meta分析

基因模型	OR(95%CI)	*P*值	I^2(%)	*P*(*Q* test)
G *vs* C	0.82(0.52-1.30)	0.41	97.0	<0.00001
GG *vs* CC	1.10(0.72-1.40)	0.97	72.0	0.001
GG *vs* GC	1.10(0.81-1.28)	0.91	65.0	0.009
GC *vs* CC	0.99(0.70-1.41)	0.96	84.0	<0.00001
GG + GC *vs* CC	1.00(0.72-1.39)	0.99	83.0	<0.00001
GG *vs* GC + CC	1.00(0.72-1.39)	0.98	63.0	0.01

表 3 Egger's线性回归检测发表偏倚结果

分组	*P*值					
	G *vs* C	GG *vs* CC	GG *vs* GC	GC *vs* CC	GG + GC *vs* CC	GG *vs* GC + CC
总体	0.054	0.656	0.400	0.954	0.953	0.274
亚洲	0.057	0.871	0.529	0.369	0.366	0.729

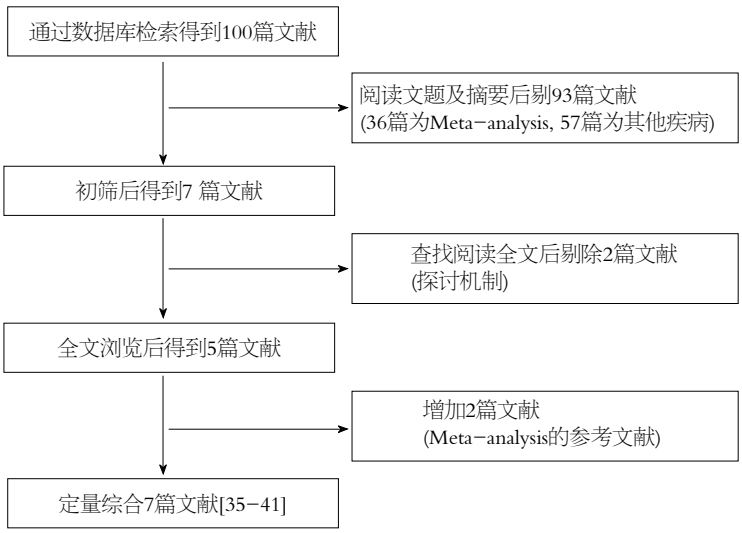

图 1 文献筛选流程.

95%CI: 0.81-1.24, *P* = 0.98. 分析结果发现, miR-146a rs2910164 G/C基因多态性与大肠癌易感性之间无关联. 为评估纳入文献的发表偏倚, 做了Begg's漏斗图及Egger's线性回归分析(表3, 图2), miR-146a rs2910164 G/C各基因模型的Egger's线性回归分析结果为*P*值均>0.05, 表明不存在发表偏倚.

3 讨论

本研究对7篇关于miR-146a rs2910164G/C基因多态性与结直肠癌易感性之间相关性的文献进行了Meta分析, 因各研究间存在显著的异质性, 因此, 采用随机效应模型对数据进行合并分析. 结果显示, 本次Meta分析未发现miR-146a rs2910164 G/C基因多态性与大肠癌易感性之间具有相关性. 亚组分析显示, 在亚洲人群中, 本次研究也未发现发表偏倚检查中发现miR-146a rs2910164 G/C基因多态性与大肠癌易感性之间具有相关性. 本研究纳入的文献不存在发表偏倚.

SNP是最常见的基因变异, 他与种族差异、疾病易感性及药物反应差异有关. 位于miRNA相关基因的单核苷酸多态性可以改变miRNA的表达量及其与目标mRNA结合的亲和力及特异性, 导致miRNA调控的靶基因mRNA的表达异常, 进而导致肿瘤等疾病的发生. 位于miR-146a前体-pre-miR-146a的单核苷酸多态性rs2910164 G/C与多种肿瘤的发生发展有关. 近年来, 关于

■创新盘点

近年来, 关于miR-146a rs2910164基因多态性与大肠癌易感性的单个研究结果不尽一致; 且相关meta分析存在纳入文献较少的缺点. 为此, 本文广泛搜集相关文献, 系统评价miR-146a rs2910164G/C基因多态性与大肠癌易感性之间的相关性.

■应用要点

单核苷酸多态性(single nucleotide polymorphism, SNP)是最常见的基因变异, 他与种族差异、疾病易感性及药物反应差异有关. 本次研究首次采用Meta分析的方法综合评价miR-146a rs2910164 G/C基因多态性与大肠癌易感性之间的相关性, 研究尚未发现miR-146a rs2910164 G/C基因多态性与大肠癌易感性之间具有相关性.

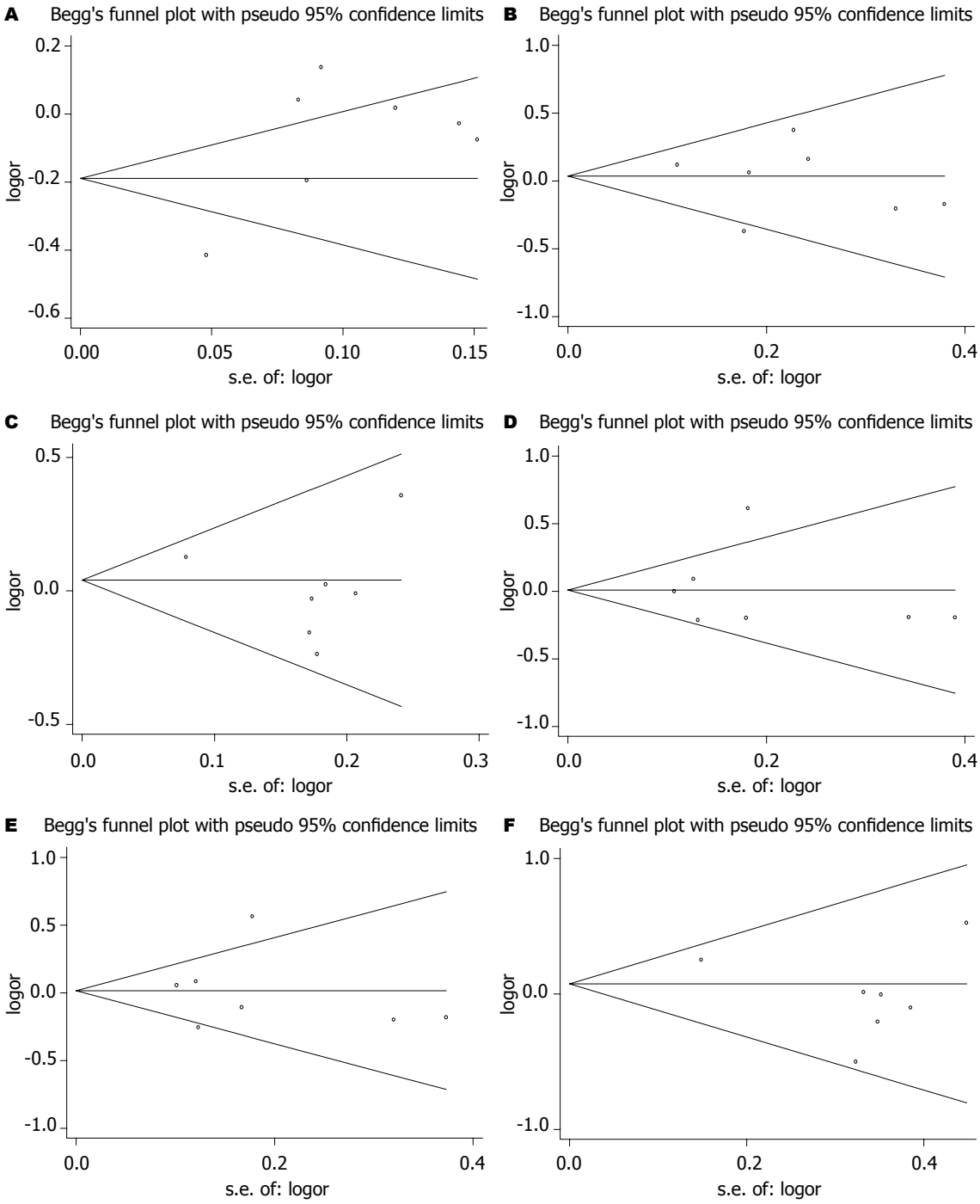

图 2 miR-146a rs2910164基因多态性与大肠癌易感性Meta分析发表偏倚结果(总体). A: G *vs* C; B: GG *vs* CC; C: GG *vs* GC; D: GC *vs* CC; E: GG + GC *vs* CC; F: GG *vs* GC+ CC.

miR-146a rs2910164基因多态性与大肠癌易感性的单个研究结果不尽一致; 且相关Meta分析存在纳入文献较少的缺点. 为此, 本文广泛搜集相关文献, 系统评价miR-146a rs2910164 G/C基因多态性与大肠癌易感性之间的相关性.

本次研究首次采用Meta分析的方法综合评价miR-146a rs2910164 G/C基因多态性与大肠癌易感性之间的相关性, 研究尚未发现miR-146a rs2910164 G/C基因多态性与大肠癌易感性之间具有相关性. 然而, 本次研究尚存在以下不足: (1)本次研究纳入的文献数量较少; (2)本次研究纳入的文献多是关于亚洲人的研究, 对于其他种族的报道则较少, 由于不同的种族具有不同的遗传背景, 其miR-146a rs2910164 G/C等位基因频率也不相同, 进而对疾病的易感性不同; (3)本次研究尚未考虑基因之间及基因与环境之间

的相互作用的影响. 这些因素的存在都会影响本次Meta分析结果的可靠性. 这些问题的解决, 有赖于开展大样本、多中心、同质性的病例对照研究, 将研究结果纳入Meta分析, 以便对miR-146a rs2910164 G/C基因多态性与大肠癌易感性的关系做出更合理、可靠的结论.

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