



doi:10.7659/j.issn.1005-6947.2021.05.007
http://dx.doi.org/10.7659/j.issn.1005-6947.2021.05.007
Chinese Journal of General Surgery, 2021, 30(5):551-557.

· 乳腺外科专题研究 ·

血清 miR-196a-5p 和 miR-339-5p 表达水平在乳腺癌诊断中的应用价值

吴衍, 高文玉, 高苏平, 李志红

(上海健康医学院附属周浦医院 普通外科, 上海 200135)

摘要

背景与目的: 研究显示, miR-196a-5p 在乳腺癌细胞中呈高表达, 而 miR-339-5p 呈低表达, 两者可能是乳腺癌潜在治疗靶点和诊断标志物。因此, 本研究探讨血清 miR-196a-5p 和 miR-339-5p 表达水平在乳腺癌诊断中的应用价值。

方法: 选择 2016 年 1 月—2017 年 6 月收治的乳腺癌患者 107 例 (乳腺癌组), 以及同期诊断为乳腺良性疾病的患者 60 例 (乳腺良性疾病组) 和健康体检者 35 例 (健康对照组), 比较各组血清 miR-196a-5p、miR-339-5p 以及乳腺癌特异性标记物 CA15-3 水平差异, 分析三者血清水平对乳腺癌的诊断效能, 并分析乳腺癌患者血清 miR-196a-5p 和 miR-339-5p 表达水平之间的关系以及两者水平与乳腺癌临床病理特征的关系。

结果: 在健康对照组、乳腺良性疾病组、乳腺癌组, 血清 miR-196a-5p 与 miR-339-5p 水平分别依次升高和依次降低, 组间差异均有统计学意义 (均 $P < 0.01$), 乳腺癌组血清 CA15-3 水平明显高于乳腺良性疾病组和健康对照组 (均 $P < 0.01$), 但后两组间差异无统计学意义 ($P > 0.05$)。血清 miR-196a-5p 和 miR-339-5p 水平诊断乳腺癌的效能均明显优于血清 CA15-3 ($Z = 2.543, P < 0.05$; $Z = 2.190, P < 0.05$), 而 miR-196a-5p 与 miR-339-5p 之间的诊断效能差异无统计学意义 ($P > 0.05$); miR-196a-5p 与 miR-339-5p 联合检测诊断乳腺癌的 AUC 为 0.937, 灵敏度与特异度分别为 91.6%、88.3%, 明显优于两者单独检测 (miR-196a-5p: $Z = 3.044, P < 0.01$; miR-339-5p: $Z = 3.020, P < 0.01$)。乳腺癌患者术前血清 miR-196a-5p 与 miR-339-5p 表达水平呈负相关 ($r = -0.764, P < 0.01$); 与术前比较, 乳腺癌患者术后血清 miR-196a-5p 水平明显降低, 而 miR-339-5p 水平明显升高 (均 $P < 0.01$)。乳腺癌患者血清 miR-196a-5p 和 miR-339-5p 水平与肿瘤直径、淋巴结转移和 TNM 分期明显有关 (均 $P < 0.01$)。

结论: 血清 miR-196a-5p 和 miR-339-5p 表达水平检测对乳腺癌有较好的诊断价值与潜在的预后监测价值, 两者诊断乳腺癌的诊断效能均优于 CA15-3, 且两者联合检测能够进一步提高对乳腺癌的诊断效能。

关键词

乳腺肿瘤; 微 RNAs; 生物标记, 肿瘤

中图分类号: R737.9

Application value of serum miR-196a-5p and miR-339-5p expression levels in diagnosis of breast cancer

WU Yan, GAO Wenyu, GAO Suping, LI Zhihong

(Department of General Surgery, Zhoupu Hospital Affiliated to Shanghai University of Medicine & Health Sciences, Shanghai 200135, China)

基金项目: 上海市自然科学基金资助项目 (18ZR1433700)。

收稿日期: 2021-01-19; **修订日期:** 2021-04-18。

作者简介: 吴衍, 上海健康医学院附属周浦医院主治医师, 主要从事乳腺外科方面的研究。

通信作者: 李志红, Email: lance007@126.com

Abstract

Background and Aims: Studies have demonstrated that miR-196a-5p expression is increased while miR-339-5p expression is decreased in breast cancer cells, so they may probably be the therapeutic targets or diagnostic markers for breast cancer. Therefore, this study was conducted to evaluate the application values of serum levels of miR-196a-5p and miR-339-5p in diagnosis of breast cancer.

Methods: One hundred and seven patients with breast cancer (breast cancer group) treated during January 2016 to June 2017, along with 60 patients with benign breast disease (benign breast disease group) and 35 individuals undergoing healthy maintenance examination (healthy control group) during the same period were enrolled. The differences of serum levels of miR-196a-5p and miR-339-5p as well as the breast cancer-specific marker CA15-3 were compared among groups, and the diagnostic abilities of serum levels of the three indices were determined. In addition, the relationship between serum levels of miR-196a-5p and miR-339-5p in breast cancer patients as well as the associations of their levels with the clinicopathologic characteristics of breast cancer were also analyzed.

Results: In healthy control group, benign breast disease group and breast cancer group, the serum levels of miR-196a-5p and miR-339-5p were successively increased and decreased respectively, and the differences between groups were all statistically significant (all $P < 0.01$). The serum CA15-3 level in breast cancer group was significantly higher than that in benign breast disease group and healthy control group (both $P < 0.01$), but the difference between the latter two groups showed no statistical significance ($P > 0.05$). The diagnostic abilities for breast cancer of both serum miR-196a-5p and miR-339-5p levels were significantly superior to that of serum CA15-3 level ($Z = 2.543, P < 0.05$; $Z = 2.190, P < 0.05$), but the diagnostic abilities between miR-196a-5p and miR-339-5p showed no significant difference ($P > 0.05$). The AUC of the combined detection of miR-196a-5p and miR-339-5p for diagnosis of breast cancer was 0.937, with the sensitivity and specificity 91.6% and 88.3% respectively, which was significantly superior to that of either lone detection (miR-196a-5p: $Z = 3.044, P < 0.01$; miR-339-5p: $Z = 3.020, P < 0.01$). There was a negative correlation between the preoperative serum expression levels of miR-196a-5p and miR-339-5p in breast cancer patients ($r = -0.764, P < 0.01$), and serum miR-196a-5p level was decreased while the serum miR-339-5p level was increased significant after surgery compared with those before surgery in breast cancer patients (both $P < 0.01$). The serum levels of both miR-196a-5p and miR-339-5p in breast cancer patients were significantly associated with tumor diameter, lymph node metastasis, and TNM stage (all $P < 0.01$).

Conclusion: The determination of serum levels of miR-196a-5p and miR-339-5p has high diagnostic value and also has a potential monitoring value for breast cancer. Both diagnostic abilities of miR-196a-5p and miR-339-5p are superior to that of CA15-3, and their combined detection can further increase the diagnostic efficacy.

Key words

Breast Neoplasms; MicroRNAs; Biomarkers, Tumor

CLC number: R737.9

乳腺癌是全球女性最常见的恶性肿瘤，其发病率位居中国女性恶性肿瘤首位^[1]。但乳腺癌往往起病隐匿，早期缺乏特异性表现，临床主要通过乳腺彩超和钼靶进行初步筛查，进而借助病理细胞学检查明确诊断，但这些方法往往导致患者错过早期诊治的重要时机^[2]。微小RNA (miRNA) 是一种由18~24个核苷酸组成的非编码蛋白RNA小分子^[3-4]，通过对靶基因的翻译抑制或切割降解来调控基因的表达，其与多种肿瘤的发生发展有关，并有研究发现某些miRNA的异常表达与乳腺癌的不良预后有关^[5-6]。通过检测多种miRNA在乳腺癌

细胞株中表达的相关研究显示，miR-196a-5p呈显著高表达^[7-8]，而miR-339-5p表达显著下调^[9]。因此，两者的生物学功能可能对乳腺癌诊断有着重要临床意义，本研究联合检测乳腺癌患者血清miR-196a-5p和miR-339-5p表达水平，观察其在乳腺癌早期诊断中的临床价值。

1 资料与方法

1.1 临床资料

选择2016年1月—2017年6月在我院就诊的

乳腺外科诊治的乳腺癌患者107例(乳腺癌组),年龄35~79岁,平均(51.28±9.65)岁;根据TNM分期标准:I期34例,II期37例,III期21例,IV期15例;病理为浸润性导管癌72例,黏液腺癌7例,导管内癌8例,小叶癌8例,髓样癌12例。纳入标准:均被病理确诊乳腺癌,女性;术前无放化疗和内分泌治疗;均接受乳腺癌的手术治疗;所有患者临床病理资料完整;无其他肿瘤病史。选择同期在我院诊断为乳腺良性疾病的患者60例(乳腺良性疾病组),年龄35~79岁,平均(52.19±10.58)岁;其中乳腺病33例,乳腺导管内乳头状瘤11例,乳腺不典型增生7例和乳腺纤维瘤9例。选择同期在我院行健康体检者35例(健康对照组),年龄35~79岁,平均(51.76±9.75)岁。所有的患者均知情同意,并签署知情同意书和经医院伦理委员会审核通过。3组在年龄等基线资料具有可比性。

1.2 方法

1.2.1 血液标本留取 患者各组入院后和乳腺癌手术后1周抽取肘静脉血10 mL。采用离心机将血液离心,离心半径15 cm,离心速度3 000 r/min,离心15 min,抽取上清液放置在除酶管内,放置在-70℃冰箱中保存。

1.2.2 qRT-PCR 总RNA抽取:采用受试者血清400 μL,采用TRIzol试剂盒进行提取血清总RNA,反转录引物有上海化生有限公司合成,miR-196a-5p上游引物序列:5'-CGC GCG TAG GTA GTT CAT GTT-3',下游引物序列:5'-CAG TGC AGG GTC CGA GGT-3'; miR-339-5p上游引物序列为:5'-GGG TCC CTG TCC TCC CCA-3',下游引物序列5'-TGC GTG TCG TGG AGT C-3'。U6的上游引物为:5'-GAG GCA CAG CGG AAC G-3',下游引物:5'-CTA CCA CAT AGT CCA GG-3'。miRNA的检测:选择反转录酶1 μL,RNA 5 μL和3 μL引物,在15 μL的反应体系中,采用美国

ABI TaqMan PreAmp Master Mix进行扩增,扩增条件为:在16℃30 min,42℃反应30 min和85℃反应5 min。取反转录配制20 μL反应体系,放置在荧光定量仪中进行反应,反应条件为:95℃预变性为15 min,94℃变性15 s,55℃退火30 s,70℃延伸30 s,连续40个循环。每个样品检测3次,以 $2^{-\Delta\Delta Ct}$ 表示。

1.2.3 观察指标 比较各组血清miR-196a-5p、miR-339-5p和乳腺癌特异性标志物CA15-3水平,三者诊断乳腺癌的效能,以及血清miR-196a-5p和miR-339-5p表达水平与临床病理特征的关系。

1.3 统计学处理

采用SPSS15.0统计分析软件对数据进行分析,呈正态分布的计量资料采用均数±标准差($\bar{x}\pm s$)进行表示,多组独立因素的计量资料采用方差分析,两组独立因素的计量资料采用t检验。采用Logistic二元回归分析得出血清miR-196a-5p和miR-339-5p联合变量,绘制出受试者曲线(ROC)评价诊断乳腺癌的效能。采用MedCalc软件计算截断值。检验水准, $\alpha=0.05$ 。

2 结果

2.1 各组血清miR-196a-5p、miR-339-5p和CA15-3水平比较

乳腺癌组血清miR-196a-5p表达水平明显高于乳腺良性疾病组和健康对照组($P<0.01$),乳腺良性疾病组明显高于健康对照组($P<0.01$);乳腺癌组血清miR-339-5p表达水平明显低于乳腺良性疾病组和健康对照组($P<0.01$),乳腺良性疾病组明显低于健康对照组($P<0.01$);乳腺癌患者血清CA15-3水平明显高于乳腺良性疾病组和健康对照组($P<0.01$),而乳腺良性疾病组和健康对照组差异无统计学意义($P>0.05$)(表1)。

表1 各组血清miR-196a-5p、miR-339-5p和CA15-3水平比较($\bar{x}\pm s$)

Table 1 Comparison of the serum levels of miR-196a-5p, miR-339-5p and CA15-3 among groups ($\bar{x}\pm s$)

组别	miR-196a-5p ($2^{-\Delta\Delta Ct}$)	miR-339-5p ($2^{-\Delta\Delta Ct}$)	CA15-3 (kU/L)
健康对照组 (n=35)	1.52±0.76	3.12±0.92	12.96±5.28
乳腺良性疾病组 (n=60)	2.75±1.07 ¹⁾	1.49±0.52 ¹⁾	14.77±10.20
乳腺癌组 (n=105)	4.84±1.60 ^{1),2)}	0.81±0.38 ^{1),2)}	25.10±11.25 ^{1),2)}
F	119.680	291.441	34.393
P	0.000	0.000	0.000

注:1)与健康对照组比较, $P<0.01$;2)与乳腺良性疾病组比较, $P<0.01$

Note: 1) $P<0.01$ vs. healthy control group; 2) $P<0.01$ vs. benign breast disease group

2.2 血清 miR-196a-5p 和 miR-339-5p 表达水平在诊断乳腺癌的效能

血清miR-196a-5p和miR-339-5p表达的诊断乳腺癌的效能明显优于血清CA15-3 ($Z=2.543$, $P<0.05$; $Z=2.190$, $P<0.05$), 而血清miR-196a-5p表达与miR-339-5p之间差异无统计学意义 ($P>0.05$), 将miR-196a-5p和miR-339-5p指标

进行二元Logistic回归得方程 $y=1.09 \times X_{miR-196a-5p} - 3.61 \times X_{miR-339-5p} + 0.66$, 联合检测 (miR-196a-5p+miR-339-5p) 的灵敏度为91.6%, 特异度为88.3%, 其AUC为0.937, 明显高于单个指标表达 (miR-196a-5p: $Z=3.044$, $P<0.01$; miR-339-5p, $Z=3.020$, $P<0.01$) (表2) (图1)。

表2 血清 miR-196a-5p、miR-339-5p 和 CA15-3 对诊断乳腺癌的诊断效能

Table 2 Diagnostic efficiencies of serum miR-196a-5p, miR-339-5p and CA15-3 for breast cancer

项目	截断值	灵敏度 (%)	特异度 (%)	AUC	95% CI
miR-196a-5p	> 3.479	84.1	80.0	0.866	0.805-0.914
miR-339-5p	≤ 1.32	94.4	65.0	0.856	0.794-0.906
CA15-3 (kU/L)	> 15.01	83.2	15.0	0.751	0.679-0.815
miR-196a-5p+miR-339-5p	—	91.6	88.3	0.937	0.888-0.969

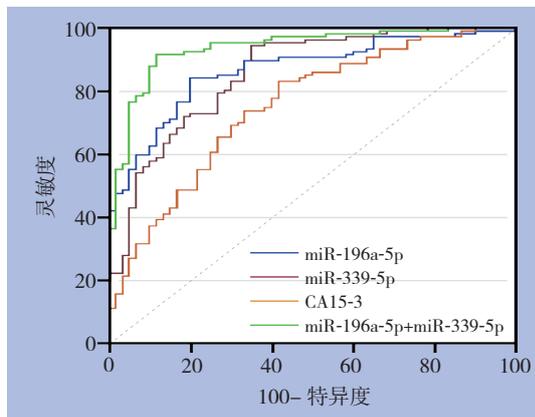


图1 血清 miR-196a-5p、miR-339-5p 和 CA15-3 在诊断乳腺癌的灵敏度和特异度

Figure 1 The sensitivities and specificities of serum miR-196a-5p, miR-339-5p and CA15-3 in diagnosis of breast cancer

2.3 乳腺癌患者术前 miR-196a-5p 和 miR-339-5p 表达的关系与术后的变化

乳腺癌患者术前血清miR-196a-5p表达与miR-339-5p呈负相关 ($r=-0.764$, $P<0.01$), 手术后乳腺癌患者血清miR-196a-5p和miR-339-5p表达分别为 1.86 ± 0.85 和 2.59 ± 0.86 , 血清miR-196a-5p表达水平较术前明显降低 ($P<0.01$), 而miR-339-5p表达较术前明显升高 ($P<0.01$)。

2.4 乳腺癌患者血清 miR-196a-5p 和 miR-339-5p 表达与临床病理因素的关系

乳腺乳腺癌患者血清miR-196a-5p和miR-339-5p表达水平与肿瘤直径、淋巴结转移和TNM分期具明显有关 (均 $P<0.01$), 而与年龄, 绝经否, 组织学分级, ER, PR和HER-2无明显关系 (均 $P>0.05$) (表3)。

表3 乳腺癌患者血清 miR-196a-5p 和 miR-339-5p 水平与临床病理因素的关系 ($\bar{x} \pm s$)

Table 3 Relations of serum levels of miR-196a-5p and miR-339-5p in breast cancer patients with clinicopathologic factors ($\bar{x} \pm s$)

因素	例数 (n)	miR-196a-5p	t	P	miR-339-5p	t	P
年龄 (岁)							
< 50	67	4.84 ± 1.63			0.81 ± 0.38		
≥ 50	40	4.83 ± 1.57	0.053	0.958	0.82 ± 0.37	0.095	0.924
绝经与否							
是	45	4.83 ± 1.56			0.82 ± 0.36		
否	62	4.84 ± 1.64	0.061	0.951	0.81 ± 0.39	0.027	0.979
肿瘤直径 (cm)							
> 2	57	6.01 ± 1.05			0.53 ± 0.20		
≤ 2	50	3.49 ± 0.91	13.136	0.000	1.14 ± 0.23	14.815	0.000
组织学分级							
I	29	5.02 ± 1.49			0.77 ± 0.35		
II	37	4.66 ± 1.74	0.426	0.654	0.85 ± 0.41	0.391	0.678
III	41	4.86 ± 1.57			0.81 ± 0.37		

表3 乳腺癌患者血清 miR-196a-5p 和 miR-339-5p 水平与临床病理因素的关系 ($\bar{x} \pm s$) (续)Table 3 Relations of serum levels of miR-196a-5p and miR-339-5p in breast cancer patients with clinicopathologic factors ($\bar{x} \pm s$) (continued)

因素	例数 (n)	miR-196a-5p	t	P	miR-339-5p	t	P
淋巴结转移							
有	55	3.54 ± 0.92	13.334	0.000	0.51 ± 0.20	14.719	0.000
无	52	6.07 ± 1.04			1.13 ± 0.23		
TNM 分期							
I	34	3.12 ± 0.88	106.742	0.000	1.25 ± 0.19	268.573	0.000
II	37	4.69 ± 0.43			0.81 ± 0.10		
III-IV	36	6.61 ± 0.87			0.40 ± 0.16		
ER							
阳性	64	4.85 ± 1.65	0.069	0.945	0.81 ± 0.38	0.126	0.900
阴性	43	4.82 ± 1.52			0.82 ± 0.37		
PR							
阳性	66	4.82 ± 1.63	0.141	0.888	0.82 ± 0.38	0.962	0.911
阴性	41	4.86 ± 1.57			0.81 ± 0.37		
HER-2							
阳性	32	4.98 ± 1.43	0.620	0.537	0.78 ± 0.33	0.650	0.517
阴性	75	4.77 ± 1.68			0.83 ± 0.39		

3 讨论

miRNA 是一类进化上保守的小分子非编码 RNA, 成熟 miRNA 通过与 mRNA 的 3' 非翻译区 (UTR) 结合诱导其降解、翻译抑制或从翻译机制中截留靶向 mRNA 来调控基因的表达^[10]。研究^[11-12]表明, 特定的 miRNA 在不同的肿瘤中出现明显的上调或下调, 可能作为肿瘤预测标志物和潜在的治疗靶点, 具有显著的临床价值。miRNA 表达具有组织特异性, 其表达差异可以区分不同分化类型的肿瘤, 也可以区分正常组织和肿瘤组织, 临床诊断中可以帮助寻找肿瘤原发病灶^[13-14]。现在其已作为某些特定肿瘤分子诊断学依据, 而且其在肿瘤治疗和预后中的作用也受到极大的关注^[15-16]。

miR-196a 是 2004 年发现的 HOX 家族基因转录而来, 在细胞分化的调节过程中扮演着重要角色, 与肿瘤的发生发展存在重要联系。现有研究显示 miR-196a 在多种肿瘤表现出类似致癌基因的生物学特性, 且降低 miR-196a 的表达具有明显抑制肿瘤增殖、转移侵袭、促进凋亡甚至有逆转耐药的作用^[12,17]。王艳等^[9]研究通过 miRNA 芯片技术检测 847 种 miRNA 在不同侵袭力乳腺癌细胞株中的表达, 获得与乳腺癌侵袭相关的 miRNA 表达谱, miR-339-5p 表达显著改变, 具有类似抑癌基因的生物学特性, 并发现 miR-339-5p 转染到乳腺癌中能够明显抑制乳腺癌的增殖和转移^[18], 两者可能成为乳腺癌诊断的重要肿瘤预测标志物。

在一项食管癌的研究证实 miR-196a 出现高

表达, 并且发现 miR-196a 能够促进肿瘤细胞的增殖和迁移, 对与预测肿瘤预后和早期诊断方面具有较高的临床价值^[19]。在对胃癌的研究中发现出现 miR-196a 高表达, 并且与肿瘤大小和肿瘤分期呈正相关, 与患者的生存期呈负相关^[20-21]。miR-196a 在结肠癌组织或者细胞系中呈高表达, 而高表达的 miR-196a 可以激活 Akt 信号通路促进结肠癌的侵袭和迁移能力, 并且增强细胞对化疗药物的耐药^[22]。本组研究显示乳腺癌组患者血清 miR-196a-5p 表达水平明显优于乳腺良性疾病组和健康对照组, 并且术后血清 miR-196a-5p 水平出现明显降低, 说明血清 miR-196a-5p 表达来源于乳腺癌细胞。miR-196a-5p 在乳腺癌的表达水平研究较少, 有研究发现通过转染 miR-196a-2 到乳腺癌细胞内, 会起到类似致癌基因的作用, 并认为 miR-196a-2 可以作为乳腺癌的新型标记物^[23]。本组研究还发现血清 miR-196a-5p 表达水平肿瘤直径, 分期和淋巴结是否转移具有显相关性, 并且发现血清 miR-196a-5p 表达量超过 3.479 ($2^{-\Delta\Delta Ct}$), 其诊断乳腺癌的灵敏度为 84.1%, 特异度 80.0%, AUC 为 0.866 具有较高的诊断效能, 可能作为诊断乳腺癌的敏感指标。

有研究^[24-26]发现 miR-339-5p 表达在胃癌、结肠癌、肺癌和食管癌等实体肿瘤中出现明显的表达异常。在一项胃癌的细胞株研究发现 miR-339-5p 出现明显的低表达, 高侵袭性的细胞株表达更低^[27]。且在结肠癌中得到同样的结论^[28], 将 miR-339-5p 转染到结肠癌细胞中, 其侵袭和增殖能力

明显降低,形成肿瘤的能力明显降低。本组研究显示乳腺癌组血清miR-339-5p表达水平明显低于良性乳腺疾病组和健康对照组,并且发现乳腺癌术后血清miR-339-5p表达水平出现明显提高,说明乳腺癌与miR-339-5p表达水平具有一定的联系,与Zheng等^[29]报道的结论接近,将miR-339-5p基因转染到乳腺癌细胞,发现在裸鼠体内成瘤的时间明显延长,充分说明miR-339-5p基因有类似抑癌基因的特性。在对抑制乳腺癌的机制研究中发现miR-339-5p可以通过抑制BCL-6水平的表达,从而抑制乳腺癌细胞的增殖和迁移^[30]。本组研究还发现乳腺癌肿瘤分期越高,淋巴结出现转移,直径越大,血清miR-339-5p表达越低,同时发现 $\leq 1.32(2^{-\Delta\Delta Ct})$ 时,其灵敏度为94.4%,特异度为65.0%,AUC为0.856,在诊断乳腺癌具有较高的诊断效能,故血清miR-339-5p可能为诊断乳腺癌的诊断指标。

本组研究发现血清miR-196a-5p表达水平与miR-339-5p表达呈负相关,并且发现血清miR-196a-5p和miR-339-5p表达水平在诊断乳腺癌的诊断效能均高于CA15-3,联合检测miR-196a-5p和miR-339-5p能够明显提高对乳腺癌的诊断效能,其灵敏度达到91.6%,特异度为88.3%,AUC明显高于单个指标,说明两指标之间存在某种互补性,故联合检测能够提高乳腺癌诊断效能,但其具体作用机制尚需进一步实验证实。综上所述,联合miR-196a-5p和miR-339-5p基因检测有助于对乳腺癌的诊断。

参考文献

- [1] 赫捷,陈万青,李霓,等.中国女性乳腺癌筛查与早诊早治指南(2021,北京)[J].中国肿瘤,2021,30(3):161-191. doi:10.11735/j.issn.1004-0242.2021.03.A001.
He J, Chen WQ, Li N, et al. China Guideline for the Screening and Early Detection of Female Breast Cancer (2021, Beijing)[J]. China Cancer, 2021, 30(3):161-191. doi:10.11735/j.issn. 1004-0242.2021.03.A001.
- [2] 黎立喜,马飞.乳腺癌筛查和早期诊断的血液生物学标志物[J].国际肿瘤学杂志,2021,48(2):109-112. doi:10.3760/cma.j.cn371439-20200629-00021.
Li LX, Ma F. Blood biomarkers for breast cancer screening and early diagnosis[J]. Journal of International Oncology, 2021, 48(2):109-112. doi:10.3760/cma.j.cn371439-20200629-00021.
- [3] 张帆,李泽东,彭禹,等.基于血清miRNA表达数据的胰腺癌诊断决策树构建[J].中国普通外科杂志,2021,30(2):211-218. doi:10.7659/j.issn.1005-6947.2021.02.010.
Zhang F, Li ZD, Peng Y, et al. Construction of decision tree for diagnosis of pancreatic cancer based on serum miRNA expression data[J]. Chinese Journal of General Surgery, 2021, 30(2):211-218. doi:10.7659/j.issn.1005-6947.2021.02.010.
- [4] 杨浚沅,王龙强,李海,等.乳腺癌循环miRNA生物标志物的筛选及验证[J].中国普通外科杂志,2015,24(5):696-700. doi:10.3978/j.issn.1005-6947.2015.05.016.
Yang JF, Wang LQ, Li H, et al. Screening and verification of circulating miRNA biomarkers of breast cancer[J]. Chinese Journal of General Surgery, 2015, 24(5):696-700. doi:10.3978/j.issn.1005-6947.2015.05.016.
- [5] Shimomura A, Shiino S, Kawauchi J, et al. Novel combination of serum microRNA for detecting breast cancer in the early stage[J]. Cancer Sci, 2016, 107(3):326-334. doi: 10.1111/cas.12880.
- [6] He Y, Deng F, Yang S, et al. Exosomal microRNA: a novel biomarker for breast cancer[J]. Biomark Med, 2018, 12(2):177-188. doi: 10.2217/bmm-2017-0305.
- [7] Shahabi A, Naghili B, Ansarin K, et al. miR-140 and miR-196a as Potential Biomarkers in Breast Cancer Patients[J]. Asian Pac J Cancer Prev, 2020, 21(7):1913-1918. doi: 10.31557/APJCP.2020.21.7.1913.
- [8] 陈晶,赵璐,宋牧,等. has-mir-125a-5p和has-mir-196a2基因多态性与新疆汉族和维吾尔族乳腺癌的相关性研究[J].重庆医学,2018,47(12):1685-1687. doi:10.3969/j.issn.1671-8348.2018.12.030.
Chen J, Zhao L, Song M, et al. Correlation of gene polymorphism of has-mir-125a-5p and has-mir-196a2 with breast cancer in the Han and Uyghur nationalities[J]. Chongqing Medicine, 2018, 47(12):1685-1687. doi:10.3969/j.issn.1671-8348.2018.12.030.
- [9] 王艳.人乳腺癌细胞侵袭相关miRNAs的筛选及hsa-miR-339-5p生物学功能的初步研究[D].合肥:安徽医科大学,2010. doi:10.7666/d.D128766.
Wang Y. The expression of hsa-miR-339-5p in breast cancer and the preliminary study of its biological behavior[D]. Hefei: Anhui Medical University, 2010. doi:10.7666/d.D128766.
- [10] Dong H, Lei J, Ding L, et al. MicroRNA: function, detection, and bioanalysis[J]. Chem Rev, 2013, 113(8):6207-6233. doi: 10.1021/cr300362f.
- [11] Piasecka D, Braun M, Kordek R, et al. MicroRNAs in regulation of triple-negative breast cancer progression[J]. J Cancer Res Clin Oncol, 2018, 144(8):1401-1411. doi: 10.1007/s00432-018-2689-2.
- [12] 高航,赵峰,吴衍,等.微小RNA-9-5p靶向HIC1降低乳腺癌细胞对多柔比星敏感性的研究[J].外科理论与实践,2020,25(3):227-233. doi: 10.16139/j.1007-9610.2020.03.011.
Gao H, Zhao F, Wu Y, et al. Study on microRNA-9-5p reducing sensitivity of breast cancer cells to doxorubicin through targeting HIC1[J]. Journal of Surgery Concepts & Practice, 2020, 25(3):227-233. doi: 10.16139/j.1007-9610.2020.03.011.
- [13] 王晓琼,张玲玲,王江洪,等. miRNA在肺癌筛查、诊断、治疗及预后中的应用价值[J].唐山师范学院学报,2017,39(5):65-68.

- doi:10.3969/j.issn.1009-9115.2017.05.019.
- Wang XQ, Zhang LL, Wang JH, et al. The Value of Mirna in the Screening, Diagnosis, Treatment and Prognosis of Lung Cancer[J]. Journal of Tangshan Teachers College, 2017, 39(5):65-68. doi:10.3969/j.issn.1009-9115.2017.05.019.
- [14] 高杰, 张晓, 魏超. 差异表达miRNA 在胰腺癌预后判断中的价值[J]. 癌变·畸变·突变, 2019, 31(3):173-179. DOI:10.3969/j.issn.1004-616x.2019.03.001.
- Gao J, Zhang X, Wei C, et al. Involvement of differentially expressed miRNA in prognosis of pancreatic cancers[J]. Carcinogenesis, Teratogenesis & Mutagenesis, 2019, 31(3):173-179. DOI:10.3969/j.issn.1004-616x.2019.03.001.
- [15] 马跃, 高英静, 何浪. 乳腺癌差异表达miRNA在预后中的意义[J]. 医学研究杂志, 2018, 47(1):39-44. doi:10.11969/j.issn.1673-548X.2018.01.011.
- Ma Y, Gao YJ, He L. Differential Expression of miRNA in Breast Cancer and the Significance in Prognosis[J]. Journal of Medical Research, 2018, 47(1):39-44. doi:10.11969/j.issn.1673-548X.2018.01.011.
- [16] 周琨, 陆霁, 殷晓星, 等. 血清miRNA-128a和miRNA-128b表达对胃癌早期诊断和预后的影响[J]. 复旦学报:医学版, 2019, 46(6):797-802. doi:10.3969/j.issn.1672-8467.2019.06.013.
- Zhou K, Lu J, Yin XX, et al. Impact of serum miRNA-128a and miRNA-128b expression on early diagnosis and prognosis in patients with gastric cancer[J]. Fudan University Journal of Medical Sciences, 2019, 46(6):797-802. doi:10.3969/j.issn.1672-8467.2019.06.013.
- [17] 姜黎黎, 万里, 王朝霞. miR-196a在肿瘤研究中的进展[J]. 现代肿瘤医学, 2015, 23(16):2389-2392. doi:10.3969/j.issn.1672-4992.2015.16.41.
- Jiang LL, Wan L, Wang ZX. Progression of miR-196 a in tumor[J]. Journal of Modern Oncology, 2015, 23(16):2389-2392. doi:10.3969/j.issn.1672-4992.2015.16.41.
- [18] 刘雪, 吴正升, 吴强. 乳腺癌细胞中miR-339-5p对BCL-6表达的调节[J]. 临床与实验病理学杂志, 2013, 29(3):244-246. doi:10.3969/j.issn.1001-7399.2013.03.003.
- Liu X, Wu ZS, Wu Q. BCL-6 is a target gene of miR-339-5p in breast cancer[J]. Chinese Journal of Clinical and Experimental Pathology, 2013, 29(3):244-246. doi:10.3969/j.issn.1001-7399.2013.03.003.
- [19] Ma Y, Wang B, Guo Y, et al. Inhibition of miR-196a affects esophageal cancer cell growth in vitro[J]. Biomed Pharmacother, 2016, 84:22-27. doi: 10.1016/j.biopha.2016.09.013.
- [20] Feng C, She J, Chen X, et al. Exosomal miR-196a-1 promotes gastric cancer cell invasion and metastasis by targeting SFRP1[J]. Nanomedicine (Lond), 2019, 14(19):2579-2593. doi: 10.2217/nmm-2019-0053.
- [21] Li HL, Xie SP, Yang YL, et al. Clinical significance of upregulation of mir-196a-5p in gastric cancer and enriched KEGG pathway analysis of target genes[J]. Asian Pac J Cancer Prev, 2015, 16(5):1781-1787. doi: 10.7314/apjcp.2015.16.5.1781.
- [22] Li S, Zhou J, Wang Z, et al. Long noncoding RNA GAS5 suppresses triple negative breast cancer progression through inhibition of proliferation and invasion by competitively binding miR-196a-5p[J]. Biomed Pharmacother, 2018, 104:451-457. doi: 10.1016/j.biopha.2018.05.056.
- [23] Jedlinski DJ, Gabrovská PN, Weinstein SR, et al. Single nucleotide polymorphism in hsa-mir-196a-2 and breast cancer risk: a case control study[J]. Twin Res Hum Genet, 2011, 14(5):417-421. doi: 10.1375/twin.14.5.417.
- [24] Li Y, Zhang X, Yang Z, et al. miR-339-5p inhibits metastasis of non-small cell lung cancer by regulating the epithelial-to-mesenchymal transition[J]. Oncol Lett, 2018, 15(2):2508-2514. doi: 10.3892/ol.2017.7608.
- [25] Huang E, Fu J, Yu Q, et al. CircRNA hsa_circ_0004771 promotes esophageal squamous cell cancer progression via miR-339-5p/CDC25A axis[J]. Epigenomics, 2020, 12(7):587-603. doi: 10.2217/epi-2019-0404.
- [26] 陈杰, 郭文超, 陈攀, 等. 干扰lncRNA RHPN1-AS1表达通过靶向miR-339-5p对肝癌细胞增殖和凋亡的影响[J]. 中国医学装备, 2021, 18(2):142-148. doi:10.3969/J.ISSN.1672-8270.2021.02.036.
- Chen J, Guo WC, Chen P, et al. Study on the effect of interfering the expression of lncRNA RHPN1-AS1 on proliferation and apoptosis of hepatoma cells by targeting miR-339-5p[J]. China Medical Equipment, 2021, 18(2):142-148. doi:10.3969/J.ISSN.1672-8270.2021.02.036.
- [27] Chen FR, Sha SM, Wang SH, et al. RP11-81H3.2 promotes gastric cancer progression through miR-339-HNRNPA1 interaction network[J]. Cancer Med, 2020, 9(7):2524-2534. doi: 10.1002/cam4.2867.
- [28] Zhou C, Lu Y, Li X. miR-339-3p inhibits proliferation and metastasis of colorectal cancer[J]. Oncol Lett, 2015, 10(5):2842-2848. doi: 10.3892/ol.2015.3661.
- [29] Zheng L, Zhang Y, Fu Y, et al. Long non-coding RNA MALAT1 regulates BLCAP mRNA expression through binding to miR-339-5p and promotes poor prognosis in breast cancer[J]. Biosci Rep, 2019, 9(2):BSR20181284. doi: 10.1042/BSR20181284.
- [30] Wu ZS, Wu Q, Wang CQ, et al. MiR-339-5p inhibits breast cancer cell migration and invasion in vitro and may be a potential biomarker for breast cancer prognosis[J]. BMC Cancer, 2010, 10:542. doi: 10.1186/1471-2407-10-542.

(本文编辑 姜晖)

本文引用格式: 吴衍, 高文玉, 高苏平, 等. 血清miR-196a-5p和miR-339-5p表达水平在乳腺癌诊断中的应用价值[J]. 中国普通外科杂志, 2021, 30(5):551-557. doi:10.7659/j.issn.1005-6947.2021.05.007
Cite this article as: Wu Y, Gao WY, Gao SP, et al. Application value of serum miR-196a-5p and miR-339-5p expression levels in diagnosis of breast cancer [J]. Chin J Gen Surg, 2021, 30(5):551-557. doi:10.7659/j.issn.1005-6947.2021.05.007