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胰腺癌早期诊断的潜在线索——新发糖尿病

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摘 要

胰腺癌是一种高度恶性的肿瘤，五年生存率仅有7.2%~9%。对无症状的个体进行筛查、早期诊断胰腺癌是改善其预后的关键。然而胰腺癌发生率相对较低，筛查仅限于高危人群。胰腺癌患者中糖尿病的比例先前已受到重视，研究表明80%的胰腺癌患者伴有糖耐量减低或糖尿病。相比于长病程糖尿病，新发糖尿病人群胰腺癌的发病率显著增加，越来越多的研究表明新发糖尿病是胰腺癌的一个重要且早期的临床表现，这为我们早期诊断胰腺癌带来了希望。然而，原发性2型糖尿病在普通人群中很常见，而胰腺癌相关糖尿病相对较少见，并且两种糖尿病目前在临床上无法区分。因此应用新发糖尿病作为筛查工具来早期诊断无症状胰腺癌的成功与否，在很大程度上取决于我们能否应用血清标志物将胰腺癌相关糖尿病与更加常见的2型糖尿病鉴别开及建立新发糖尿病患者中胰腺癌高危人群的临床预测模型。

关键词

胰腺癌，糖尿病，早期诊断，预后

The Potential Clue for Early Diagnosis of Pancreatic Cancer—New-Onset Diabetes

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Abstract

Pancreatic cancer is a highly malignant tumor with a five-year survival rate of only 7.2% to 9%.

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Screening asymptomatic individuals and early diagnosis of pancreatic cancer is the key to improving their prognosis. However, the incidence of pancreatic cancer is relatively low, and screening is limited to high-risk groups. The proportion of diabetes in patients with pancreatic cancer has previously been valued, and studies have shown that 80% of pancreatic cancer patients have impaired glucose tolerance or diabetes. Compared with long-course diabetes, the incidence of pancreatic cancer in patients with new-onset diabetes is significantly increased. More and more studies have shown that new-onset diabetes is an important and early clinical manifestation of pancreatic cancer, which brings hope for our early diagnosis of pancreatic cancer. However, primary type 2 diabetes is common in the general population, while pancreatic cancer-related diabetes is relatively rare, and the two types of diabetes are clinically indistinguishable. Therefore, the success of using new-onset diabetes as a screening tool for early diagnosis of asymptomatic pancreatic cancer depends to a large extent on whether we can use serum markers to distinguish pancreatic cancer-associated diabetes from the more common type 2 diabetes and to establish a clinical predictive model for patients with new-onset diabetes at high risk of pancreatic cancer.

Keywords

Pancreatic Cancer, Diabetes Mellitus, Early Diagnosis, Prognosis

1. 引言

胰腺癌的发病率在全球范围内呈上升趋势，已成为癌症相关死亡的主要原因之一。对高危人群进行筛查是改善这种难治性恶性肿瘤预后的基础。糖尿病通常被认为是胰腺癌发病的危险因素。最近，逆向因果关系备受关注，也就是说，糖尿病被认为是胰腺癌的一种临床表现。大量流行病学研究表明，新发糖尿病(≤2 年病程)在胰腺癌患者中占主导地位，胰腺癌发病的相对风险与糖尿病病程呈负相关。在新发糖尿病患者中，高龄发病、体重减轻和血糖控制迅速恶化是提示胰腺癌发病的高危因素。几项初步研究揭示了金属蛋白酶 9、泛酰巯基乙胺酶等生物学标记物可能用于区分与胰腺癌相关的糖尿病和 2 型糖尿病。然而，需要更多研究来评估这些生物学标志物在实践中的应用价值。

2. 早期发现胰腺癌的必要性

胰腺癌是一种高度恶性的肿瘤，世界范围内其发病率正逐渐增加。在美国癌症相关死亡中胰腺癌排在第三位[1]，在日本排在第四位[2]，我国每年有 13.4 万新发病例，位列恶性肿瘤发病率第 7 位[3]。胰腺癌预后极差，五年生存率在 7.2%~9% [4] [5]，主要由于胰腺癌早期阶段缺乏特异性症状，80%~85%的患者确诊时已处于晚期阶段[6]。尽管较大胰腺癌(>30 mm)切除后 5 年总生存率仅为 10%~20%，但微小胰腺癌(≤10 mm)切除后 5 年生存率超过 75% [7] [8]。虽然美国预防和筛查特别工作组目前不建议对普通人群进行胰腺癌筛查[9]，但是现有的共识更倾向于对有家族史或其它高危特征的高风险人群进行早期胰腺癌筛查[10]，国际胰腺癌筛查联盟建议对于那些有家族风险的人，监测不应早于 50 岁或比最年轻的胰腺癌亲属早 10 岁开始，首选的检测是超声内镜和 MRCP。中华医学会胰腺疾病协作组在 2021 年中国胰腺癌高危人群早期筛查和监测共识意见中推荐腹遗传性胰腺癌高危个体、新发糖尿病、慢性胰腺炎、胰腺囊性肿瘤这 4 类高危人群进行胰腺癌早期筛查[11]。目前选择高危人群并对其进行筛查仍是改善胰腺癌预

后的关键。

3. 胰腺癌与糖尿病的流行病学研究

自 20 世纪 80 年代以来，已经有调查研究显示糖尿病与胰腺癌风险之间的关系[12] [13] [14]。Pannala, R 等[15]应用空腹血糖诊断糖尿病，在他们的研究中，几乎一半的胰腺癌患者伴有糖尿病，大约 85%的患者有空腹血糖受损，这一数据表明胰腺癌患者中葡萄糖利用障碍这一现象非常普遍。与此同时，糖尿病患者与健康人群相比，胰腺癌发病率明显增加。最近几个基于行政数据库或癌症/糖尿病登记的队列研究大体上证实了糖尿病和胰腺癌之间的直接联系，即无论糖尿病病程，发生胰腺癌的相对危险度都在 2.0~3.0 左右，这些研究在样本量和样本代表性方面有着重要优势[16]-[20]。对胰腺癌发病风险和糖尿病病程的进一步研究表明，长病程糖尿病患者发生胰腺癌的风险轻度增加[21] [22]，而新发糖尿病人群，胰腺癌的发病率显著提高[23] [24] [25] [26]。这表明，相比于长病程糖尿病，新发糖尿病可能是早期无症状胰腺癌潜在的临床标志，并有望应用于胰腺癌的早期筛检。

4. 胰腺癌和新发糖尿病的因果关系

糖尿病一直以来被认为是胰腺癌的病因，但越来越多的研究表明新发糖尿病是胰腺癌的一个重要且早期的临床表现[27] [28] [29]。这一观点得到了以下事实的支持，即不仅胰腺癌患者中糖尿病的患病率非常高[30] [31]，而且糖尿病的发病与胰腺癌的诊断之间存在密切的时间关系[27] [30] [32]。Ben 等[33]提供了胰腺癌风险与糖尿病持续时间之间关系的重要证据。在他们的荟萃分析中，病程 ≤1 年的糖尿病患者胰腺癌的发病率最高(RR = 5.38 95% CI, 3.49~8.30)，随着糖尿病持续时间 RR 逐渐降低，1~4 年为 1.95 (95% CI, 1.65~2.31)，5~9 年为 1.49 (95% CI, 1.05~2.12)，而超过 10 年的为 1.47 (95% CI, 0.94~2.31)。

胰腺癌引起新发糖尿病的机制目前并不清楚。一种可能解释是，糖尿病的发生是由于肿瘤浸润和导管阻塞引起的胰腺腺体破坏的结果。如果是这样的话，与没有糖尿病的胰腺癌患者相比，患有糖尿病的胰腺癌患者将肿瘤范围应该更大，分期应该更晚，更常见于胰岛细胞更加丰富的胰体和胰尾。但 Guo 等[34]的研究表明胰腺癌患者中糖尿病的发生率并不受肿瘤的分期和部位的影响，且胰腺癌伴糖尿病患者和单纯胰腺癌患者肿瘤的大小并无差异。另一种可能的解释是糖尿病的发生是胰腺癌引起的一种伴癌综合征，即肿瘤释放某种介质阻碍胰岛素的分泌或干扰胰岛素发挥作用[35]。在一项对 41 名接受胰十二指肠切除术的胰腺癌伴糖尿病患者的研究中，Pannala 等[15]注意到在 30 例新发糖尿病患者中，17 例血糖在术后得以好转，而 11 例长期患有糖尿病的患者的血糖状况均无改善。胰腺癌细胞系上清液具有新陈代谢活性，通过产生可溶性因子导致人和大鼠胰岛 β 细胞功能障碍，在体外损害葡萄糖代谢，在体内引起高血糖[35] [36] [37]，他们也能在体外诱导大鼠肝细胞和肌母细胞产生胰岛素抵抗[38] [39]。因此，目前更倾向于胰腺癌分泌某种物质，引起伴癌综合征，导致胰岛 β 细胞功能障碍及机制胰岛素的分泌，从而引起糖尿病[40]。

5. 新发糖尿病作为胰腺癌早期诊断的线索

对早期胰腺癌监测的第一步是确定一个相比于普通人群胰腺癌发病率明显增加的高危人群。Pannala 等[41]收集了 2122 名年龄 ≥50 岁的新发糖尿病患者信息，并以此为基础进行基于人群的队列研究。最终 18 名(0.85%)新发糖尿病患者发展为胰腺癌，是健康人群患胰腺癌风险的 6~8 倍。最近的研究表明，与胰腺癌相关的糖尿病患者中有一半以上是新发糖尿病[27] [28] [30] [42]。Mizuno 等[24]曾报道对于没有腹痛、黄疸、食欲减退等症状的胰腺癌患者，新发糖尿病可能是唯一的临床线索。此外，一些研究表明，糖尿病甚至在早期胰腺癌中也很普遍[8] [30] [43] [44]，一项针对微小胰腺癌的研究显示糖尿病患病率达 33%

[7]。由于近一半的早期可切除肿瘤患者患有糖尿病，因此，新发糖尿病作为胰腺癌的高发人群未来可能应用于胰腺癌的早期筛检。

要让糖尿病作为一种有效的筛查工具，它应该为无症状个体提供早期发现胰腺癌的机会之窗。由Sharma 等[45]进行的病例对照研究表明，血糖升高比胰腺癌的诊断早 30~36 个月。根据 Pelaez-Luna 等[46]的研究，从糖尿病发病到胰腺癌诊断的平均间隔为 10 个月(范围 5~29 个月)。然而相对于糖尿病发病率，胰腺癌发病率则低得多，因此是否应在所有新发糖尿病患者中进行胰腺癌的大规模筛查仍有待讨论[6]。尽管目前还没有生物标记物被证实可以区分 2 型糖尿病和癌症相关糖尿病，但有证据表明某些分子具有潜在的相关性[47]。最有说服力的包括 VNN1 [48]、肾上腺髓质素[37]、胰高血糖素/胰岛素比值[49]以及对营养摄取有缺陷的胰多肽(PP)反应[50]等。为了对新发糖尿病患者进行有效筛查，未来仍需进一步研究确定更为特异性的危险因素及生物标志物。

6. 新发糖尿病患者发生胰腺癌的危险因素

之前的研究已经报道了新发糖尿病患者发生胰腺癌的危险因素，主要包括体重减轻及血糖控制迅速恶化等[35]。高龄是另一个被广泛接受的危险因素，糖尿病 ≥65 岁发病的人群患胰腺癌的相对危险为 2.01 (95% CI, 1.51~2.68)，≥70 岁的人群 RR 为 4.52 (95% CI, 1.61~12.74)。吸烟和饮酒是胰腺癌常见的危险因素，研究表明这些危险因素与糖尿病在导致胰腺癌方面有协同作用[51] [52]。体重减轻是胰腺癌伴糖尿病的另一常见征兆，尽管体重减轻也见于 2 型糖尿病，但 Hart PA 等[53]发现胰腺癌伴糖尿病的人群在糖尿病发病时体重减轻较 2 型糖尿病患者更加明显(59% vs. 30%, $p = 0.02$)。血糖控制不佳也会增加患胰腺癌的风险，Huang BZ 等[54]的研究表明新发糖尿病伴胰腺癌的人群与单纯新发糖尿病人群相比血糖(37.47 mg/dL vs 27.68 mg/dL, $p < 0.01$)及 HBA1c (1.39% vs 0.86%, $p < 0.001$)在糖尿病诊断前升高更快。综合分析各种危险因素可能有助于在新发糖尿病患者中确定高危人群，从而实现胰腺癌的早期诊断。

7. 识别新发糖尿病患者中胰腺癌发病高危人群的临床预测模型

目前已经多项研究开发并验证了临床预测模型，以从那些新诊断糖尿病患者中识别进行胰腺癌筛查可能受益的高危人群。Borsi 等[55]对 109,385 名新发糖尿病患者进行了回顾性队列研究，并总结了一个由 11 个因素组成的预测模型，包括年龄，BMI，BMI 变化，吸烟，使用质子泵抑制剂和降糖药物以及 HbA1c，胆固醇，血红蛋白，肌酐和碱性磷酸酶的水平。这一模型的曲线下面积为 0.82，如果将三年内发生胰腺癌的风险预测阈值设为 1%，只有 6.19%的新发糖尿病人群需要进行筛检，其敏感性为 44.7%，特异性为 94%，阳性预测值为 2.6%。Sharma A 等[56]通过 1561 名新发 DM 患者进行了回顾性队列研究，开发了一种更简单的临床预测模型，称为 END-PAC 模型，该模型仅包含 3 个因素：体重变化，血糖变化和发病年龄。这一模型的曲线下面积为 0.87，在验证队列中，END-PAC 得分 ≥3 可识别出胰腺癌的敏感性为 78%，特异性为 82%，END-PAC 得分 ≥3 的人群胰腺癌发生率是 ≤0 分的人群的 4.4 倍(0.82% vs. 3.6%)。尽管这些临床模型在区分新发 2 型糖尿病和胰腺癌引起的糖尿病方面初步显示了令人鼓舞的结果，但在应用于临床之前还需要进一步的验证。

8. 基于新发糖尿病人群的胰腺癌早期筛检策略

为了充分利用新发糖尿病作为早期诊断胰腺癌线索的潜力，必须筛查个体是否有无症状的糖尿病，而不是被动的等待有症状的糖尿病被诊断出来。美国糖尿病协会(ADA)当前建议所有个体都应从 45 岁开始每 3 年进行一次糖尿病筛检[57]。新发糖尿病患者是应该用 CT 或 EUS 直接筛查胰腺癌，还是应该接受二次筛查以进一步丰富可能发生胰腺癌的人群，目前仍有争议。Pelaez-Luna 等[46]所进行的回顾性研

究表明新发糖尿病患者在胰腺癌确诊前 6 个月内无法在 CT 上发现肿瘤的存在。因此，想要在无症状个体中确认胰腺癌的存在可能需要更加激进的检查手段，如 EUS。然而，应用更加激进的手段对所有新发糖尿病患者进行胰腺癌筛查收益不会太高，因为这一人群中胰腺癌的患病率不到 1% [26]。更重要的是，即使在没有临床疾病的情况下，EUS 也可以发现异常，特别是在老年患者、吸烟者和酗酒者中[58]。这种情况下可能会引起人们对癌症存在或不存在的怀疑，并可能进一步导致不必要的胰腺切除，这是对家族性胰腺癌进行筛检的前车之鉴[59]。因此新发糖尿病人群应该接受二次筛检，筛检标准可以是症状、临床表型或胰腺癌独特的生物标志物。有两项前瞻性研究利用症状和 CA19-9 作为二次筛检标准，在新发糖尿病患者中筛查胰腺癌。虽然接受筛查的人群中胰腺癌的患病率很高(6/115, 5/36)，但大多数确诊的癌症是无法切除的，这再次重申了这样一个事实，即胰腺癌的筛查必须在没有症状的个人中进行。在缺乏可以将胰腺癌相关糖尿病与 2 型糖尿病区分开的临床特征的情况下，需要血清学或分子标记物来识别新发糖尿病患者胰腺癌的高危人群。基质金属蛋白酶 9 基因(MMP-9)在新发糖尿病相关胰腺癌患者外周血单个核细胞表达量明显升高，或可作为新发糖尿病患者筛查胰腺癌的标志物[60]。泛酰巯基乙胺酶(VNN1)在新发糖尿病相关的胰腺癌组织中呈强阳性表达，而癌旁组织与单纯胰腺癌的癌组织均呈阴性。联合分析 VNN1 和 MMP-9 在外周血基因的表达最具预测价值，其对糖尿病相关胰腺癌的敏感性和特异性分别为 95.8%和 76% [61]。但是，这些初步发现仍有待进一步研究确认。

9. 展望

胰腺癌的早期诊断对改善预后而言至关重要，为此，筛查需要针对无症状的个体。几乎所有胰腺癌患者中都存在新发糖尿病，各种证据表明，新发糖尿病是由癌症引起，然而胰腺癌相关糖尿病的发病机制仍有待阐明。目前的研究表明，糖尿病的发生可能与肿瘤分泌某些介质引起 β 细胞功能障碍有关。未来的研究可能会进一步完善高危人群预测模型和敏感的生物标志物，以鉴定新发糖尿病患者中的隐匿性胰腺癌，并为新发糖尿病患者开发一种有效且收益高的筛查方案。

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