

胆管癌危险因素研究进展

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摘要

胆管癌是一种来源于肝内或肝外胆管上皮的恶性肿瘤, 通常其在早期阶段基本没有症状, 如果不做肝脏影像学检查, 很难得到早期诊断。临床上诊断的基本都到了疾病晚期, 失去手术机会, 基本不能进行根治性手术, 其预后极差。除了一些患有原发性硬化性胆管炎、肝吸虫感染、先天性胆道畸形等, 实际上大多数没有明确的危险因素, 需进一步了解胆管癌的流行病学和危险因素, 以期早期发现, 从而改善临床治疗的效果。就目前的研究现状, 有相应危险因素的患者, 定期肝脏影像学检查可能是早期发现胆管癌最有效的方法。

关键词

胆管肿瘤, 流行病学, 危险因素, 综述

Research Progress on Risk Factors of Cholangiocarcinoma

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Abstract

Cholangiocarcinoma is a malignant tumor arising from intrahepatic or extrahepatic bile duct epithelium. Due to absence of early-stage symptoms, it often remains undiagnosed until advanced stages of disease without liver imaging scan, which limits opportunities for successful radical surgery. Cholangiocarcinoma is associated with poor prognosis. Although some risk factors are ac-

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cepted, such as primary sclerosing cholangitis, clonorchiasis, and congenital biliary malformation, most patients with cholangiocarcinoma do not have clear risk factors, further study on the epidemiology and risk factors of cholangiocarcinoma is needed in order to improve the clinical treatment effect. According to the present study, regular liver imaging scan may be the most effective method for early detection of cholangiocarcinoma in patients with corresponding risk factors.

Keywords

Cholangiocarcinoma, Epidemiology, Risk Factors, Review

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1. 胆管癌的流行病学

胆管癌(cholangiocarcinoma, CCA)是一种罕见的胆管系统恶性肿瘤,近年来发病率呈上升趋势,根据肿瘤与二级胆管的解剖位置,分为肝内胆管癌和肝外胆管癌,肝外胆管癌包括肝门胆管癌和远端胆管癌[1]。而肝内胆管癌是仅次于肝细胞癌的第二常见的原发性肝恶性肿瘤,占有癌症死亡病例的3%。根据截至2020年的统计数据,近几十年来,全球胆管癌的发病率在全球范围内有所增加(每年0.3~6/10万人);死亡率也在增加(每年1~6/10万人),胆管癌高度流行的东部国家(即泰国、中国、韩国)的死亡率尚未报告。由于环境和遗传因素的地理差异,胆管癌的流行病学在全球范围内是不同的,发病率的变化反映了各地区或国家的危险因素和遗传倾向的差异性[1][2][3][4]。除了不同的危险因素、病理分子学、临床表现、治疗和预后外,胆管癌的三个亚型似乎显示出不同的流行趋势。肝门胆管癌和肝内胆管癌的真实发病率尚不清楚,因为在许多数据库中肝门胆管癌被错误地归类为肝内胆管癌[5][6]。这种错误编码可能使肝内胆管癌的上升率显而易见。因此,在未来几年,新的国际疾病分类和对危险因素的了解将使我们能够对这种癌症的流行病学获得更准确的数据,这对于更好地了解其发病机制和改进诊断和治疗策略将非常有用。

2. 危险因素

2.1. 明确的危险因素

2.1.1. 原发性硬化性胆管炎

原发性硬化性胆管炎(primary sclerosing cholangitis, PSC)是一种胆汁淤积性肝病,其特征是胆道系统纤维化炎症损伤,诱导慢性炎症、胆管上皮增殖和内源性胆汁诱变剂的产生,可能导致胆管肿瘤发生[7]。PSC是胆管癌发生的公认危险因素之一,胆管癌是原发性硬化性胆管炎患者最常见的恶性肿瘤,也是导致死亡的主要原因,许多专家认为PSC是癌前状态,因为10%到20%的PSC患者会发展为胆管癌[8]。由于胆管癌的临床表现无特异性,基于人群的研究表明,27%至37%的胆管癌是在PSC诊断后一年内被发现的[9],目前越来越多的人认识到与PSC相关的胆管癌是一个重要的危险因素,因此,可以确定明确的高危人群,以制定有效的监测及管理计划。

2.1.2. 肝吸虫感染

由华支睾吸虫(*C. sinensis*)或麝猫后睾吸虫(*O. viverrini*)引起的肝吸虫感染是东亚和东欧主要地区的

公共卫生问题, 约 11 亿人存在感染风险[10]。人类感染通常通过摄入生的、腌制或未煮熟的食物而发生。虽然肝吸虫感染可以用吡喹酮治疗, 但个体往往会再次感染, 而且多次再感染可能比单一的长期感染更有害。胆管癌是肝吸虫感染导致的最严重的并发症, 东南亚国家尤其是泰国的肝内胆管癌发病率居全世界首位。因此, 国际癌症研究署明确将华支睾吸虫列为 I 类致癌物[11]。迄今为止, 只有华支睾吸虫和麝猫后睾吸虫在动物研究中被证明会导致慢性胆管炎症和胆管周围瘢痕形成, 从而增加胆道恶性肿瘤的风险[12]。尽管只有不到 10% 的肝吸虫病感染会发展为胆管癌, 但胆管癌的高发病率与肝吸虫感染的高流行率有关[13]。

2.1.3. 肝胆管结石疾病

肝胆管结石是世界性的疾病, 主要见于东南亚和东亚国家, 在西方很少见, 但随着胆结石疾病模式的改变, 其发病率在西方国家也在增加, 发病率从 2% 到 25% 不等[14]。肝胆管结石本质上是良性的, 但由于与胆管炎反复发作、胆道狭窄有关, 预后较差, 甚至形成肝脓肿或肝硬化。肝内胆管结石也是肝内胆管癌的已知危险因素[13]。肝内胆管结石与肝内胆管癌之间的关联已得到充分证明, 许多关于肝内胆管结石相关的胆管癌的研究已发表[15] [16] [17]。肝外胆管结石, 尤其是胆总管结石与肝外胆管癌的风险增加有关, 最近一项基于美国 Surveillance Epidemiology End Results (SEER) 的数据库分析报告了肝外胆管癌发展与肝外胆管结石之间的明显关联[16]。在肝胆管结石的治疗中, 重要的是减少胆管炎的复发和识别早期的肝内胆管结石相关的胆管癌。

2.1.4. 先天性胆管疾病

胆管癌与先天性胆管疾病之间也有关联, 包括先天性胆管扩张(胆总管囊肿)、胰胆管连接不良和 Caroli 病。胆总管囊肿是一种罕见的先天性胆道疾病, 其特征是胆管的囊性扩张。在亚洲国家, 尤其是中国和日本的女性胆管囊肿发病率较高, 而西方人群则相对较低[18]。胆管囊肿和胆管癌之间的相关性已得到充分证实, 肝内胆管癌和肝外胆管癌的总风险均会增加[19]。Caroli 病是一种罕见的先天性疾病, 其特征为肝内胆管的非阻塞性节段性囊性扩张, 已被纳入 V 型胆管囊肿的分类[20]。据报道, Caroli 病是肝内胆管癌和肝外胆管癌的最高危险因素, 使肝内胆管癌的风险增加 38 倍, 肝外胆管癌的风险增加 97 倍[19]。其中的 Caroli 病的癌变率为 2.5%~16%, 而约 18% 的胆管囊肿患者存在恶变风险。Caroli 病和胆管囊肿与三种胆管癌亚型密切相关[16] [19]。

2.2. 尚未明确的危险因素

2.2.1. 病毒性肝炎

病毒性肝炎感染是世界范围内的一个主要公共卫生问题。据报道, 乙型肝炎病毒(hepatitis B virus, HBV)和丙型肝炎病毒(hepatitis C virus, HCV)感染是慢性病毒性肝炎的两个主要原因。许多研究发现 HBV、HCV 感染也是胆管癌发展的一个重要危险因素, 尤其与肝内胆管癌的关联性更强[21]。然而, 乙肝病毒或丙型肝炎病毒感染与胆道癌之间的关系仍然知之甚少。在西方人群中, 肝内胆管癌与丙型肝炎的感染关联性更强, 在亚洲人群中, 这种恶性肿瘤与乙型肝炎的感染关联性更强[21]。这些结果表明, 不同地区地方性肝炎病毒类型的不同可能决定了胆管癌危险因素的差异性。一项针对亚洲患者的病例对照研究提示肝硬化患者中将会使胆管癌发生风险增加[22]。HBV 和 HCV 患者的发生胆管癌的风险可能不仅取决于肝硬化的存在, 还取决于这些病毒对靶细胞的直接致癌作用; 而且病毒感染导致肝脏慢性炎症, 释放炎症细胞因子, 诱导肝纤维化, 增强细胞增殖和产生基因毒性活性氧从而导致癌变可能[23]。

2.2.2. 代谢性和内分泌相关疾病

非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)包括一系列临床肝病, 从肝脂肪变性开

始可能发展为非酒精性脂肪性肝炎(Non-alcoholic steatohepatitis, NASH), 肝硬化甚至肝细胞癌[24] [25]。最近, Kinoshita 等人发现 NASH 是肝内胆管癌的独立危险因素[26]。此外, 尽管一些研究已经提供了非酒精性脂肪性肝炎、肥胖症和 II 型糖尿病作为单一病因增加胆管癌风险的作用, 但由于缺乏数据, 这些疾病对增加胆管癌的风险仍存在分歧。在最近的一项国外研究报道了 II 型糖尿病与两种胆管癌类型, 尤其是肝内胆管癌之间的正相关关系[19]。糖尿病和胆管癌之间的潜在关联可能是直接的或由其他中间危险因素介导的, 例如肥胖或非酒精性脂肪肝病, 目前尚不清楚; 多项研究报道肥胖与不同类型的胆管细胞癌呈正相关[27] [28] [29], 但肥胖在胆管癌发展中的作用仍然存在争议, 目前的证据有限, 无法得出可靠的结论。全球肥胖和非酒精性脂肪肝病的人数增加可能是导致肝内胆管癌发病率上升的原因, 但大多数胆管癌患者没有明确危险因素[30]。

2.2.3. 炎症性肠病和其他

炎症性肠病(inflammatory bowel disease, IBD), 即溃疡性结肠炎和克罗恩病被广泛认为是肠癌的危险因素[31] [32]。根据最近的一项荟萃分析, IBD 患者发生胆管癌的风险也会增加[33], 溃疡性结肠炎和克罗恩病都被发现与胆管癌风险增加有关, 但与溃疡性结肠炎的相关性更强[34] [35], 这两种病理状态都可能与慢性炎症和/或微生物群失调导致胆管癌的发生有关[36]。炎症性肠病也可能有肠外表现, 包括原发性硬化性胆管炎, 这是众所周知的胆管癌危险因素[37]。炎症性肠病与胆管癌相关, 但目前还没有充分的证据。另外其他报道的危险因素还包括酒精和烟草, 虽然酒精和烟草是许多癌症的公认的危险因素, 但他们与胆道肿瘤的关系仍不清楚。流行病学研究表明, 胆管癌与暴露于某些环境致癌物之间存在正相关[38]。据报道, 暴露于放射造影剂二氧化钍的受试者患胆管癌的风险比普通人增加了 300 倍[39]。然而, 由于这种化合物自 1969 年以来一直被禁用, 目前与二氧化钍放射剂接触有关的胆管癌的数量可以忽略不计。Sato 等人报道了在日本大阪印刷厂的工人胆管癌的高发病率; 该疾病与长期接触的有机溶剂有关, 研究人员将这些病例归类为职业性接触相关胆管癌[40]。最近, 一项病例对照研究提供了石棉暴露与胆管癌之间的联系, 报告了长期接触石棉会使肝内胆管癌发生风险增加, 且接触时间越长, 发病风险越高[41]; 表明石棉可能是肝内胆管癌的危险因素。

3. 胆管癌的治疗策略

胆管癌是一种侵袭性强、预后差的恶性肿瘤。目前胆管癌的治疗方法仍以手术切除为主, 根据美国癌症协会的数据, 非侵入性肝内胆管癌和肝外胆管癌的 5 年生存率分布为 15% 和 30%, 而两种转移亚型的 5 年生存率显著下降至 2% [42]。对不适合手术或局部治疗的晚期胆管癌患者, 可选择化疗方案。除了手术治疗和化疗之外, 分子靶向治疗、免疫治疗也是较好的治疗手段, 目前正处于临床试验研究的多种靶向治疗药物及免疫治疗药物都在进行临床试验。临床疗效还有待大样本、对照研究验证, 为改善胆管癌患者的生存提供了希望。

4. 小结

与胆管癌相关的危险因素很多, 但大多数病例与任何已知的危险因素没有确定性。胆管癌的发病率呈上升趋势, 因为缺乏其他亚型的数据库, 尚不能确定是否与肝门胆管癌相关, 代谢综合征和其他新发现的胆管癌危险因素可能是全球胆管癌患病增加的原因之一。今后应对这一类患者增加更多的关注, 因此需要对肝胆管中潜在的致病机制进一步研究, 除流行病学数据外, 还包括遗传学和基础科学研究, 肿瘤免疫微环境是治疗胆管癌的潜在靶点。目前, 胆管癌的组织学分类尚无国际共识, 仍需对这些肿瘤的命名和诊断标准进行标准化。对于胆管癌手术完全切除, 包括高度选择的病例肝移植, 仍是胆管癌唯一根治的方法。然而由于胆管癌早期没有临床症状、体征, 如果患者不进行定期的体格检查, 很难得到早

期诊断, 切除只适用于少数病例。因此, 提倡患者建立病例档案, 定期规律检查, 尤其是目前确认高危因素的患者, 更应该定期进行包括彩色 B 超、CT 和磁共振等在内的影像学检查, 尽早发现早期患者, 才可能提高临床治疗效果, 延长生命, 提高生存率。

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