

肾细胞癌的高危因素

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摘要

肾细胞癌是一种常见的恶性肿瘤,在美国,肾细胞癌的发病率在男性中占据第六位,女性中占据第十位,其中在男性和女性患者所有肿瘤中分别占据3%和5%。在过去20余年中,肾细胞癌的诊断和治疗水平不断进步,但是肾细胞癌仍然是泌尿系统中最致命的恶性肿瘤之一。随着医学水平的进步以及在诊疗过程中影像学检查使用的推进,越来越多的患者存在偶发肾细胞癌的现象。虽然偶发的肾细胞癌检测出的病灶大多都是小肿瘤,但是仍有17%的患者在发现时伴有远处转移。因此肿瘤的预防和通过早期筛查发现肾癌,对于患者的预后是极有好处的。通常在组织学上,肾细胞癌会分为透明细胞癌,乳头状肾细胞癌,嫌色细胞癌,肾集合管癌和未分类细胞癌,其中最为常见的类型为透明细胞癌,其次为乳头状肾细胞癌。由于肾透明细胞癌通常在晚期发现,所以肾透明细胞癌的特异生存率最差。为了进一步保护大众生命健康,探究影响肾癌的高危因素,本文就肾癌的危险因素进行综述。

关键词

肾细胞癌, 高危因素

Risk Factors of Renal Cell Carcinoma

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Abstract

Renal cell carcinoma is a common malignant cancer, in the United States, the incidence of renal cell carcinoma in male is sixth, up the tenth of women, which in all patients with cancer in both

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men and women occupies 3% and 5% respectively. In the past 20 years, the level of diagnosis and treatment of renal cell carcinoma continues to advance, but renal cell carcinoma is still one of the most fatal tumors in urinary system. With the progress of medical level and the advancement of imaging examination in the process of diagnosis and treatment to use, the phenomenon of incidental renal cell carcinoma exists in more and more patients. Although sporadic renal cell carcinoma detected lesions are mostly small tumors, but there are still 17% of the patients with distant metastasis when found. Therefore kidney cancer prevention and the early screening are of great benefit to the prognosis of patients. Usually on histology, renal cell carcinoma was divided into clear cell carcinoma, papillary renal cell carcinoma, suspicion color cell carcinoma, renal collecting duct carcinoma and unclassified cells, among which the most common type is clear cell carcinoma, followed by papillary renal cell carcinoma. Due to renal clear cell carcinoma usually found in the late, so the specific survival rate of the renal clear cell carcinoma is the worst. In order to further protect the public life and health, to explore the risk factors of influence of kidney cancer, this paper summarized risk factors of the kidney cancer.

Keywords

Renal Cell Carcinoma, High Risk Factor

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1. 引言

肾脏是维持人体体液和溶质稳态平衡的重要器官, 它还有助于调节血压, 并分泌激素[1] [2] [3]。肾脏由肾实质和集合系统组成。实质包括外层皮质和内层髓质。集合系统包括肾盂和肾盏, 肾盏由移行细胞排列。发生于肾实质的成人肾癌主要是腺癌, 也称为肾细胞癌, 而发生于集合系统的主要是移行细胞癌。肾细胞癌占成人肾癌的 90%以上[4]。在这篇综述中, 我们将重点关注成人肾癌, 讨论肾细胞癌的危险因素。

2. 糖尿病

糖尿病是一种常见的以慢性高血糖为特征慢性代谢性疾病, 在成人中, 糖尿病患者约占 5% [5], 随着病情进展, 会对心脏、肾脏、血管、眼睛等造成严重危害, 其中与肥胖有关的 2 型糖尿病约占所有病例的 90%, 2 型糖尿病其病理生理机制为过量的有理化脂酸和促炎细胞因子增加引起胰岛素抵抗, 当最初产生胰岛素抵抗时, 胰腺通过分泌更多的胰岛素进行补偿, 然而随着胰腺 β 细胞的退化, 糖尿病随之进展[6]。

目前研究现状表明糖尿病有多种途径可促进肾细胞癌进展, 其一是 Warburg 假说: 癌细胞在线粒体中获取能量的途径更加倾向于糖酵解, 而不是通过氧化呼吸链, 因此癌细胞为了维持正常的新陈代谢, 需要大量的葡萄糖供应其能量, 而糖尿病患者体内的高糖环境恰好符合这一高糖条件。其次, 高血糖还可以通过增加蛋白激酶 C 和过氧化物酶体增殖物激活受体(peroxisome proliferators-activated receptors, PPARs)水平进一步促进肿瘤细胞增殖[7]。其二是负责生长、增殖、细胞调节的哺乳动物雷帕霉素通路学说, 蛋白激酶 B 调节大多数细胞通路, 其中包括肾癌的发生。在一项研究中, 研究人员分别检测了患有肾细胞癌的患者和肾细胞癌同时患有糖尿病的患者, 发现第二组的癌细胞的活性明显提高[8]。结节蛋白

是急性肾衰竭时释放的一种抑制生殖过程引起增殖的蛋白质, 而蛋白激酶 B 负责结节蛋白的磷酸化或失活, 因此激活了雷帕霉素通路, 进而激活 p70 核糖体蛋白 S6 激酶蛋白的磷酸化。磷酸化的 p70 核糖体蛋白 S6 激酶在有糖尿病的肾细胞癌患者和仅有肾细胞癌的患者中, 其在前者中有所升高[8]。因此可以得出糖尿病患者的蛋白激酶 B 活性增加, 结节蛋白浓度降低, 最终导致雷帕霉素通路活性增加, 以上这一系列过程都在影响癌细胞的增殖。其三是高胰岛素血症和胰岛素样生长因子有关的学说。胰岛素促进胰岛素样生长因子-1 的合成及提高其活性, 而胰岛素和胰岛素样生长因子-1 都能促进细胞增殖并且抑制细胞的凋亡, 胰岛素样生长因子通过具有酪氨酸激酶活性的跨膜蛋白胰岛素样生长因子-1 受体发挥作用。胰岛素样生长因子-1 受体通过激活磷脂酰肌醇 3 激酶和丝裂原活化蛋白激酶传递信号[9], 同时它也存在肾细胞癌患者的细胞中[10]。在某些增殖增强的细胞中, 胰岛素样生长因子-1 受体通常位于核膜中, 从而实现直接的转录调控[11]。但是这种说法具有争议的, Aleksic 等人[11]认为位于核膜上的胰岛素样生长因子-1 受体导致细胞增殖增强, 预后较差, 但是 Lkhagvadorj 等人[12]的研究中发现胰岛素样生长因子受体-1 在恶性程度较低的肿瘤(Fuhrman 分级量表)中表达增加, 并认为这一结果不适用于高级别肿瘤。而 Rasmuson 等人[13]的研究结果表明, 胰岛素因子-1 水平的升高与较好的预后有关($P = 0.017$)。因此, 综合上述观点, 糖尿病的患者患有肾细胞癌的风险更高。

3. 高血压

原发性高血压是以体循环动脉血压增高为主要特征的一种复杂、进行性发展的心血管综合征。高血压作为一种威胁人类健康的常见慢性病, 在近年来呈现一种不断上升的趋势[14]。目前研究认为高血压是引起肾细胞癌的危险因素[15], 在高血压进展过程中, 肾素-血管紧张素系统发挥着关键作用, 血管紧张素 II 为该系统的核心, 同时在现有研究中发现血管紧张素 II 亦可通过调节黏附、迁移、侵袭、增殖和血管生成的途径在各种癌症中发挥关键作用[16]。

为了进一步验证高血压是肾癌的危险因素, Liam C. Macleod 等人[17]通过前瞻性的队列研究调查了 2000 年至 2002 年期间的 77260 名华盛顿居民得出高血压是肾细胞癌的危险因素这一结论。但是在近些年研究成果中很少有涉及高血压是否影响肾细胞癌的发展和预后。为了进一步研究高血压对于肾癌进程的影响, 日本一个团队对此展开一项回顾性分析, 该团队分析回顾了 2007 年 10 月至 2018 年 12 月的 462 例确诊肾细胞癌的患者, 得出高血压组肿瘤大小明显小于非高血压组(中位数分别为 32 mm, 45 mm, $P = 0.010$), 高血压组的 5 年癌症特异性和无转移生存率显著优于非高血压组(分别为 93.6%和 80.4%, 84.6%和 73.0%, $P = 0.021$ 和 $P = 0.017$) [18]。

综上所述, 我们可以得出高血压虽然是肾细胞癌的危险因素, 但是相对于非高血压人群的肾细胞癌患者, 肾细胞癌合并高血压的人群有着更好的预后。

4. 肥胖

超重和肥胖患者在世界范围内不断增加, 世界卫生组织表示, 自从 1975 年以来, 人群的肥胖率增加了两倍[19]。近些年来的流行病学研究表明, 肾细胞癌的病因体重是其中很重要的因素[20]。

脂肪组织作为哺乳动物最大的内分泌器官, 产生的激素统称为脂肪因子。肥胖的患者相比于正常体重患者其中的一些激素水平会较高, 比如瘦素和白细胞介素-6, 这些激素具有促进肿瘤产生的作用[21]。其次, 脂肪组织还会分泌一种具有生理活性的多肽-脂联素, 该激素对肾癌会产生抑制作用[22], 但是其激素水平与体重呈负相关。

虽然肥胖对于高血压、冠心病等慢性疾病产生影响, 会使结果产生偏移, 但是仍有充分的流行病学证据证实了二者关系。在美国的一项长达 16 年, 对 90 多万美国人进行的前瞻性的队列研究, 结果证实

了超重的男性和女性发生肾细胞癌的风险分别增加了 1.7 倍和 4.75 倍[23]。同样是前瞻性的队列研究, Liam C. Macleod 等人的亦得出相同的结果[17]。

5. 吸烟

全球范围内, 吸烟人口众多, 大概有 20% 的人类吸烟, 同时吸烟人数也是逐年增加, 从 1980 年的 4.96 亿人增加到 2016 年的 5.5 万亿[24]。国际癌症研究机构已将吸烟列为肾癌发展的危险因素[25]。

4-(甲基亚硝胺)-1-(3-吡啶)-1-丁酮(NNK)是香烟烟雾中含量最丰富的致癌亚硝胺之一。4-[(乙酰氧基甲基)亚硝胺]-1-(3-吡啶基)-1-丁酮(NNKOAc)是 NNK 前体, 能够反应人类对 NNK 敏感性[26]。Jessica Clague 等人发现肾细胞癌患者的外周血淋巴细胞样本比有着更大的 DNA 损伤, 并且 NNKOAc 诱导 DNA 损伤水平的升高与肾细胞癌风险显著增加相关[26]。为了探究 NNK 与肾细胞癌的关系, 中国的一个团队筛选出在实验室条件下暴露于 NNK 的肾细胞癌细胞所表达的基因特征, 其中包括 ANKRD1、CYB5A、ECHDC3、MT1E 和 AKT1S1, 并发现这新的基因特征与 TNM 分期, 浸润深度, 转移和肿瘤分级显著相关[27]。

路易斯安那州立大学研究人员一项 Meta 分析发现随着吸烟数量的增加, 肾癌与吸烟呈现一个明确的风险剂量-反应模式, 同时 10 年或 10 年以上的长期戒烟者, 戒烟可以减轻肾细胞癌的患病风险[28]。晚期肾细胞癌为转移性疾病, 病理分期 $\geq T3$ 期和(或)淋巴结受累[29]。来自美国杜克大学医学中心的一个团队回顾性分析了 10 年期间接受肾细胞癌手术的患者, 发现重度吸烟与晚期肾癌风险增加相关[29]。综上所述, 吸烟是肾细胞癌的一项危险因素, 而戒烟能明显降低患有肾细胞癌的风险。

6. 肝炎

丙型肝炎病毒在世界范围内, 尤其是发展中国家, 是影响人类健康的常见病毒, 丙型肝炎病毒是肝癌的一项危险因素, 而近几年的研究也发现丙型肝炎病毒同样也是肾细胞癌的一个风险因素[30]。

Viroj Wiwanitkit 等人通过生物信息学技术, 通过发现丙型肝炎与肾癌共同相关蛋白进而寻找二者之间关系, 发现丙型肝炎病毒相关蛋白和肾细胞癌相关蛋白组之间只有一种常见的蛋白质为 NY-REN-54。通过 NY-REN-54 推测丙型肝炎病毒感染与肾细胞癌之间可能存在因果关系, 丙型肝炎病毒导致肾癌这一过程可能与泛素-蛋白连接酶相关机制干扰自噬反应有关[30]。

Stuart C. Gordon 等人[31]通过对 1997 年至 2006 年期间接受丙型肝炎病毒检测的 67063 的患者进行队列研究, 最终得出慢性丙型肝炎病毒感染是肾细胞癌的风险因素这一结论。由此可见, 丙型肝炎病毒感染同样也是肾细胞癌的高危因素。

7. 国家地区与人种

7.1. 国家与地区

在世界范围内, 北美洲的发病率最高, 其次是西欧和澳大利亚[32]。亚洲国家肾细胞癌的发病率比其他地区低[33]。对于全世界范围内的国家来说, 捷克共和国的肾细胞癌的发病率最高[34]。Shalini Agnihotri 等人[35]通过对印度肾细胞癌的研究, 发现相对于发达国家, 印度的肾细胞癌的发病年龄更早, 同时有着更晚的临床分期。

在同一国家不同地区中, 发病率也是不尽相同, KEN MARUMO 等人[36]对全日本的肾细胞癌发病率进行研究, 发现北海道地区的肾细胞癌的发病率明显高于日本其他地区。

7.2. 人种

Jie Lin 等人[37]发现与白人相比, 黑人患有肾透明细胞癌, 肾嫌色细胞癌的可能性更低, 但是肾乳头

状细胞癌并未表现出明显差异,Wong-Ho Chow 等人[38]也得出相同的结论,但是不同的是 Wong-Ho Chow 等人认为肾乳头状细胞癌在黑人中更为常见,虽然白人患者的 5 年生存率比黑人较高(分别为 72.6%, 68%),但是同一种族中未接受手术的患者相较于接受肾切除的患者,白人与黑人的生存率相似。Alyssa C. Dobyns 等人[39]发现当患者确诊肾细胞癌时,非西班牙裔的黑人相较于非西班牙裔的白人通常是较早期的肾细胞癌,非西班牙裔美国印第安人和阿拉斯加本地人在诊断肾透明细胞癌时,有更高几率为晚期,西班牙裔在诊断肾乳头状肾细胞癌时有更高几率为晚期。E.C.L. Wong 等人发现加拿大土著居民相较于非加拿大土著居民在更年轻的年纪被诊断为肾细胞癌,并同时有着更高的转移率[40]。

8. 年龄

大多数癌症发生在 60 岁以上的人群中,随着世界人口寿命的延长和老龄化,癌症正成为一个重大的公共卫生问题,癌症和衰老的机制都是基于细胞损伤呈现时间依赖性,衰老的许多特征与癌症是相同的,包括表观遗传的变化,细胞内通讯的改变,蛋白质内稳态的改变,线粒体功能障碍[41]。

肾透明细胞癌作为肾细胞癌中发病率最高的病理类型,Xiao Feng 等人[42]对肾透明细胞癌与年龄的关系进行了研究,发现肾透明细胞癌的发病率随着年龄的增长而增加,在 60 至 79 岁的人群中达到峰值,在 ≥ 80 岁的人群中下降。Jamil S. Syed 等人[43]发现在儿童和青少年中肾细胞癌是较少见的,但是儿童肾细胞癌的发病率随着年龄增长而增加,并且占大于 12 岁儿童肾脏恶性肿瘤的 50%以上。Grégory Verhoest [44]等人发现与老年患者相比,年轻患者诊断的肾细胞癌的特点是肿瘤分期和分级较低,组织学类型较好,但是有研究对于印度人群呈现出相反的结论[35]。

9. 性别

男性比女性更常被诊断为肾细胞癌,然而这种差异背后的机制仍然是没有明确的解释[45]。Pierorazio 等人[46]通过 Meta 分析发现男性性别会使恶性组织概率增加 2.7 倍。Geolani W. Dy 等人[47]通过基于人群的研究发现男性患肾细胞癌的风险是女性的 1.85 倍。Monish Aron 等人[48]通过美国 SEER 数据库 (Surveillance Epidemiology and End Results, SEER)对性别对于肾细胞癌的影响做出分析,得出男性比女性有着更高级别的肾细胞癌,虽然女性的总体生存率更高,但是癌症特异性生存率没有明显差异。

10. 酒精

第一项关于酒精的致癌作用探索性研究可以追溯到 20 世纪初,当时报告了因为饮酒导致癌症死亡率增高[49]。有证据表明,控制饮酒可以预防癌症的发生[50],虽然早在 30 余年前,世界卫生组织已经将酒精设为致癌物[51],但是酒精与肾细胞癌的相关性与之不同[52]。Jung Eun Lee 等人[53]通过前瞻性的研究发现每天至少 15 g 的饮酒可以降低肾细胞癌 28%的风险。一项 Meta 分析评估了 23 种恶性肿瘤与饮酒的关系,指出肾细胞癌与饮酒之间存在明显的统计学负相关性[54]。

11. 环境

越来越多的人认识到污染物和环境暴露对人类疾病的影响,但由于测量和报告等方面的执行难度以及不同的地理风险因素,许多污染物的影响难以在流行病学的研究中评估。虽然研究有限,但是 X 射线、 γ 射线以及包括砷、无机砷化合物、镉、全氟辛酸、焊接烟雾、硝酸盐及饮用水中的氡在内的工业制剂仍有证据表明不是肾癌的高危因素[55] [56] [57] [58]。虽然肾细胞癌不是一种职业病,但是仍有关于某些职业和某些化工产物接触有关的报道产生。国际研究机构认为三氯乙烯是一种可能致癌的化学物质,同时也是迄今为止与肾细胞癌相关的研究中最广泛提及的化学物质[59],三氯乙烯与肾细胞的流行病学关系的证据逐渐积累,越来越多的研究表明三氯乙烯的接触水平与肾细胞癌发病率呈正相关[60] [61]。但是因

为研究的局限性, 迄今为止二者尚未建立因果关系[60] [61] [62] [63]。

12. 总结

综上所述, 影响肾细胞癌的因素是多方面的, 尤其是生活中常见的慢性病, 除了常规的查体对肾细胞进行早发现, 早诊断, 早治疗外, 保持健康的生活方式, 控制血压、血糖、体重同样重要。

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