

子宫肌瘤的流行病学特征及危险因素

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摘要

子宫平滑肌瘤是全球育龄期妇女最常见的盆腔肿瘤。目前子宫肌瘤的确切病因尚未明了, 其可能的危险因素包括年龄、非裔美国人种族、肥胖、未生育、生活方式及内外源性激素因素等。本综述通过分析现有文献资料, 通过流行病学研究阐明子宫肌瘤的易感因素, 以期为探索子宫肌瘤的病因以及预防措施提供线索。

关键词

子宫肌瘤, 流行病学, 危险因素

Epidemiology and Risk Factors of Uterine Leiomyomata

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Abstract

Uterine leiomyoma is the most common pelvic tumor in women of reproductive age worldwide. The exact cause of uterine fibroids is unknown, but possible risk factors include age, African American race, obesity, childlessness, lifestyle, and exogenous hormonal factors. Through analyzing the existing literature, this review elucidates the susceptibility factors of uterine fibroids through epidemiological studies, in order to provide clues for exploring the etiology and preventive measures of uterine fibroids.

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Keywords

Uterine Leiomyomata, Epidemiology, Risk Factor

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1. 引言

子宫平滑肌瘤(Uterine leiomyomata, UL), 通常称为“肌瘤”, 是子宫平滑肌的良性肿瘤。子宫肌瘤的发病率较高, 影响全球约 70% 以上的女性, 尤其是有色人种女性[1] [2] [3]。迄今为止, 对子宫肌瘤发生和发展的相关机制了解有限, 雌、孕激素被认为是肌瘤生长的促进剂[4] [5]。子宫肌瘤常无明显症状, 但亦可引起月经过多、盆腔疼痛, 并继发贫血和不孕等。子宫肌瘤引起了重大的社会健康和经济负担, 有症状的肌瘤会严重降低女性生活质量, 是子宫切除术的主要指征, 也是生殖功能障碍的主要来源。在美国, 每年有超过 20 万例需要手术治疗的肌瘤, 每年与子宫肌瘤相关的医疗保健费用估计约为 340 亿美元[6]。在这种高患病率, 高症状负担和治疗方案有潜在不良反应的背景下, 寻找可改变的暴露因素来减少肌瘤的患病率很重要, 同时更深入地认知子宫肌瘤的病因和子宫肌瘤复杂的发病机制可以促进新的靶向治疗的进展。

2. 年龄

肌瘤不会在青春期之前发生, 其发病率随着生育年龄的增长而增加, 尤其是绝经前和 ≥ 40 岁的女性。一项关于年轻非洲裔美国人子宫肌瘤的发病率和生长的前瞻性研究表明, 随着年龄的增长, 肌瘤的发病率从 23~25 岁的 6% 增加到 32~35 岁的 13% [7]。既往文献提示, 年龄可能是子宫平滑肌瘤最重要的危险因素, 可能与患者年龄的增加、内源性雌激素的积累、免疫系统的变化以及持续暴露于环境危险因素有关[8] [9]。

3. 种族

不同种族患子宫肌瘤的风险不同。黑人女性子宫肌瘤的发病率几乎总是显著高于其他种族; 而白人、西班牙裔和亚洲女性的发病率相似[10]。子宫肌瘤在非裔美国妇女中的发病率是白人妇女的 2~3 倍[10], 肌瘤相关症状也更严重, 这可能是由于非裔美国妇女体内类固醇激素浓度较高, 也可能是由于基因多态性, 包括儿茶酚 - 氧化 - 甲基转移酶(COMT)编码基因[11]。

4. 肥胖

研究发现肥胖与肌瘤发病率增加存在关联。一项对 22 项研究的荟萃分析, 包括 325,899 名参与者和 19,593 例病例, 发现肥胖与肌瘤的风险或患病率呈正相关, 且这种关联是非线性的[12]。肌瘤的风险随着体重的增加而增加: 每增加 10 公斤, 风险增加约 21% [13]。肥胖通过多种机制影响子宫肌瘤的发病: 一种机制涉及内分泌反应, 即肥胖产生多余的脂肪组织, 并增加循环中的雄激素通过脂肪组织中的芳香化酶向雌激素的转化[14], 从而使肌瘤的平滑肌细胞的增殖增加和细胞外基质过量产生[15]; 另一种机制表明, 肥胖有可能减少肝脏分泌性激素结合球蛋白, 这种蛋白质可以结合大部分循环激素, 从而减少激素对敏感组织的影响, 而肥胖患者体内激素结合蛋白(性激素结合球蛋白)分泌的减少将导致外周末结合的雌激素水平升高[16]。

5. 心理压力因素

慢性心理压力是子宫肌瘤的环境危险因素[17],其相关机制尚未完全阐明。从生物学上讲,压力可能引起雌激素和孕激素水平的波动,这两种激素在子宫肌瘤的发展中都很重要,这是由下丘脑垂体肾上腺轴的应激激活和随后应激激素皮质醇的释放引起的[18][19]。在一项关于黑人妇女健康研究中,肌瘤诊断的高峰年龄似乎因教育水平而异,与所有其他受教育程度的组相比,有17年以上受教育程度的妇女在超声检查或子宫切除术确诊的病例中诊断的高峰年龄更早(35~39岁)[20]。在日本的一项关于环境暴露与子宫平滑肌瘤的风险的流行病学调查中发现,高中以上学历人群子宫平滑肌瘤患病率高于高中以下学历人群[21]。迄今为止,关于压力在不同种族妇女子宫肌瘤发展中的作用的研究有限,需要更多的研究来了解两者之间的关系。

6. 饮食习惯

食物成分可能与子宫肌瘤的发生风险有关。根据流行病学证据,特定的饮食成分和营养具有影响激素相关疾病的潜在能力,高纤维饮食和低脂肪饮食都会降低血清雌激素水平,可能是通过改变粪便菌群和减少雌激素的肠肝循环,因此影响肌瘤的形成和生长[22][23]。研究表明,与食用红肉相比,食用更多绿色蔬菜、水果和鱼的女性较少被诊断为子宫肌瘤[24][25],水果的相关性更强,尤其是富含柑橘类水果,子宫肌瘤的风险降低幅度最大[26]。牛奶或大豆中含有丰富的动、植物雌激素样物质,可发挥雌激素样功能,频繁食用牛奶或大豆是子宫平滑肌瘤发生的独立危险因素[27]。一项研究发现,食用豆浆的女性患子宫肌瘤的风险是不食用豆浆的女性的2.5倍。然而,一项研究报告子宫肌瘤与整体乳制品消费没有明确的关联,而另一项研究发现酸奶消费和从食物中摄取钙可以降低子宫肌瘤发展的风险[28]。

7. 维生素 D 水平

研究发现,子宫肌瘤在非裔美国妇女有较高的发病率与更严重的临床表现,可能与维生素D缺乏有关[29][30]。维生素D是对人体内具有多效性固体影响的脂溶性类固醇化合物的总称,其在人体皮肤中由7-脱氢胆固醇在暴露于阳光下合成。维生素D被认为可以调节细胞增殖和分化,抑制血管生成,刺激细胞凋亡,它在预防癌症、调节免疫系统和控制各种内分泌系统方面具有多种功能[31][32][33]。Merja Blauer Ph.D.的体外研究发现子宫肌瘤组织是维生素D的敏感靶器官,它们的细胞生长受到体外生理性维生素D浓度的有效抑制[34]。维生素D水平在世界各地、不同人群和个体之间存在很大差异,年龄、种族、健康状况,甚至衣着都会影响皮肤产生维生素D的速度,主要是因为皮肤暴露于紫外线B(UVB)辐射、皮肤合成效率、膳食补充和食品加工方法存在很大差异,这使得肤色较深的人需要更长时间的阳光照射来产生足够的维生素D[35][36]。大约80%的非裔美国女性缺乏维生素D,而白人女性只有20%[37]。在患有子宫肌瘤的女性中,血清VitD水平与肌瘤疾病的严重程度呈负相关,血清VitD水平越低,肌瘤总体积越大,反之亦然,这表明补充维生素D可能是治疗子宫肌瘤的一种新的治疗选择[38]。

8. 初潮年龄与月经周期

流行病学研究表明初潮年龄与子宫平滑肌瘤呈负相关[9][39][40][41][42]。Apter对年龄在12~20岁(平均年龄16岁)的芬兰妇女初潮后的激素进行了分析,发现12岁前初潮的受试者在月经周期的第6~9天E2浓度高于月经初潮较晚的受试者[43]。初潮年龄越早,雌二醇和雌酮水平越高,性激素结合球蛋白水平越低[44][45]。相对而言,月经初潮早或绝经晚的妇女一生中受排卵周期的影响会增加,即初潮年龄较早的女性平均月经周期更长,一生中接触到的雌激素也更多。

肌瘤与月经周期模式之间的关系不太清楚。Chao-RuChen和Buck报道,在白人女性中,月经量大与

子宫肌瘤的风险增加有关, 月经周期长、出血时间长(>6 天)的白人妇女发生子宫肌瘤的风险高于出血时间短的白人妇女[46]。在护士健康研究 II 中, 不规则的月经周期和较长的月经周期长度与降低肌瘤风险相关[42], 但在以前的研究中没有发现这种关联[41] [47]。但值得注意的是, 月经出血持续时间较长可能是肌瘤生长的一种临床症状, 可能与病因无关。

9. 产次

大量研究发现, 产次与子宫肌瘤风险呈反比关系[9] [40] [42]。与未产妇女相比, 已产妇女发生子宫平滑肌瘤的风险降低, 并且在大多数研究中, 风险似乎随着孩子数量的增加而降低。一些研究人员观察到女性首次妊娠的年龄、上次足月分娩年龄及上次足月分娩后的年数与肌瘤风险呈负相关[40] [48]。目前生育对于子宫肌瘤的保护作用机制知之甚少, 一些理论认为第一或第二次怀孕后内分泌谱发生了改变, 特别是孕晚期、分娩期和产后, 可能是由于泌乳抑制了垂体激素的分泌, 随着产后子宫复旧, 平滑肌瘤开始出现血管变性, 因缺乏营养而出现萎缩[48]。此外, 产后哺乳可以延缓月经, 抑制卵巢性激素分泌, 进一步促进平滑肌瘤缩小。其他类固醇激素或其他细胞过程可能产生的影响也应予以考虑, 例如, 孕激素在怀孕期间达到高水平, 抑制子宫收缩, 维持子宫肌组织处于静止状态。

10. 口服避孕药(Oral contraceptive, OCs)

在临床研究中, 使用口服避孕药与子宫肌瘤发病率之间的关系存在许多相互矛盾的结果。一些病例对照和队列研究发现, 与“从不”使用者相比, OCs 似乎抑制了肌瘤的发病率, 且随着口服避孕药使用年限的增加, 风险也会降低, 特别是对于高剂量黄体酮的制剂[13] [40] [49] [50]。然而, 其他研究发现使用口服避孕药与平滑肌瘤的风险之间很少或没有关联, 且不止有一项研究显示, 年轻时服用口服避孕药与风险增加有关[9] [40]。子宫肌瘤与口服避孕药的负相关被解释为无拮抗雌激素理论, 即子宫没有暴露于生理增殖期的雌激素中。OCs 是否会增加肌瘤的风险主要取决于雌激素或黄体酮的成分, 以大剂量雌激素为主的 OCs 可增加肌瘤发病率, 反之可降低发病率, 而黄体酮可降低雌激素与肌瘤之间的生物学效应, 从而抑制平滑肌瘤的生长。

11. 遗传因素

肌瘤家族史似乎也是一个主要的风险因素。一级亲属患子宫肌瘤的风险加倍; 如果子宫肌瘤发生在双胞胎中的一个, 同卵双胞胎比异卵双胞胎的风险更高。

12. 高血压与糖尿病

有研究者提出“子宫肌瘤动脉粥样硬化假说”, 像高血压一样, 肌瘤是一种平滑肌细胞疾病, 血压升高可引起平滑肌细胞损伤和细胞因子释放, 并通过类似于动脉平滑肌细胞动脉粥样硬化改变的过程增加平滑肌瘤的风险[51]。大量研究发现, 高血压与肌瘤呈正相关[51]-[56], 且其中两项病例对照研究发现, 与未经治疗的高血压相比, 接受治疗的高血压患者患肌瘤的风险更高, 高血压女性(定义为收缩压 ≥ 140 mmHg, 舒张压 ≥ 90 mmHg 或目前使用抗高血压药物)发生 UFs 的风险比血压正常的女性增加了近 5 倍[53]。在一项针对美国黑人女性的大型前瞻性队列研究中, 高饮食血糖指数和血糖负荷可能与一些女性患肌瘤风险增加有关[57]。此外, 在一项胎儿期和早期生活暴露与子宫平滑肌瘤的关系的姐妹研究中, 母亲患有孕前糖尿病可能会增加成年早期肌瘤的发展[58]。

13. 激素替代疗法

激素替代疗法(Hormone replacement therapy, HRT)是治疗绝经期许多衰弱症状的有效方法, 目前 HRT

对妇女子宫肌瘤生长影响的相关研究较少, 基于子宫肌瘤对性类固醇的敏感性, 它在肌瘤患者中的应用存在广泛的争议。一项为期 3 年的前瞻性临床研究结果表明, 绝经后接受激素替代疗法的妇女有肌瘤生长增加的趋势[59], 但未能证明肌瘤的大小明显增加[59] [60] [61]。多项研究调查发现, 绝经后 HRT 期间不同的激素治疗对绝经期无症状肌瘤妇女的子宫肌瘤的体积和大小有不同的影响。研究替博龙(第二代选择性雌激素受体调节剂(SERM_s))的作用表明, 使用该药物不会导致无症状肌瘤的大小显著增加, 并可能使绝经妇女肌瘤的大小减小[62] [63] [64]。一些研究发现雌激素和黄体酮联合使用对子宫肌瘤扩大以及绝经期新发现肌瘤的频率有显著影响[65] [66] [67]。

14. 结论

在过去几年, 我们对类固醇激素、危险因素、干细胞、遗传学和表观遗传学在子宫肌瘤的发育起源和发病机制中的相互作用的研究取得了相当大的进展。在这篇综述中, 我们单独考虑并讨论了与肌瘤相关的危险因素或诱发因素, 任何减少子宫肌层暴露于雌激素或增加黄体酮水平的因素, 如使用 OCs、产次或吸烟, 都倾向于降低疾病的风险, 但事实上, 一个或多个因素之间往往存在重叠或相互作用, 例如肥胖、饮食和运动。其次, 我们只能推测这些危险因素与肌瘤发生之间的机制联系。虽然许多这些因素的影响通常归因于它们对雌激素和孕激素水平或代谢的影响, 但证明这种联系是困难的, 而且很可能涉及其他机制。且因为很少进行大型流行病学研究及肌瘤无症状病例的高患病率, 对肌瘤危险因素的分析存在局限性, 并且报告很容易存在偏差。再者, 由于目前研究中对年龄、胎次和种族以外的肌瘤的危险因素的数据缺乏, 控制肌瘤研究中的混杂因素仍然具有挑战性。因此仍然需要更多高质量的前瞻性观察数据来更好地探索子宫肌瘤发病相关的危险因素, 以期对临床预防和及时发现治疗肌瘤提供有用的信息。

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